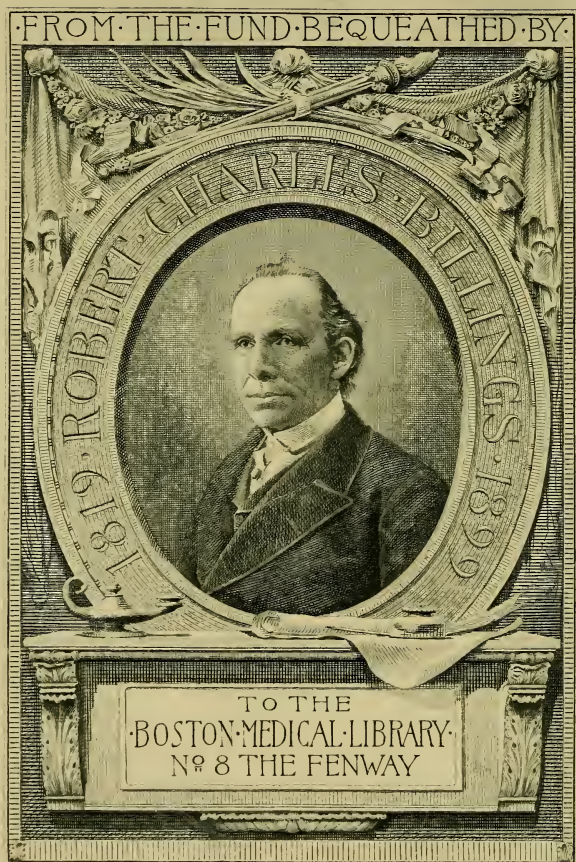




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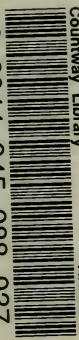
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# THE EXPERIMENTAL PROPHYLAXIS OF SYPHILIS.

BY

DR. PAUL MAISONNEUVE.

CONTAINING THE RESULTS OF THE EXPERIMENTS ON THE  
SUBJECT CARRIED OUT AT THE PASTEUR INSTITUTE BY

PROFESSORS METCHNIKOFF AND ROUX.

TRANSLATED, AND WITH AN INTRODUCTION BY

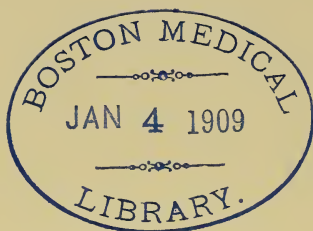
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NEW YORK:  
WILLIAM WOOD AND COMPANY.

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MDCCCXVIII.



*J. D.*  
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TO PROFESSOR GAUCHER,  
who did us the honour of accepting the presidency  
of this thesis.

TO PROFESSORS METCHNIKOFF AND ROUX.

We shall always have a pleasant and lasting recollection of those few months of daily intercourse, which enabled us to appreciate in them the spirit of the man, as well as the learning of the scientist.

In offering ourselves for experimental purposes, we believe to have given them the best proof of that confidence which a life, honestly and entirely devoted to the interests of science, can inspire.

TO DR. PAUL SALMON,  
who was always ready to place himself at our disposal,  
and to help us with his advice.

TO DRS. SABOURAUD AND QUEYRAT,  
who were willing to give to this experiment the support of their great authority on skin and venereal diseases.





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## INTRODUCTION.

THE successful inoculation of the anthropoid apes with syphilis in 1903 by Metchnikoff and Roux, and the subsequent discovery in 1905 by Fritz Schaudinn of the *Spirochæta pallida*, or *Treponema pallidum* as it was subsequently called, have opened up a new era in the study of a disease which for centuries has proved one of the greatest scourges of the human race.

These discoveries have stimulated research and excited such great interest, that rarely has such scientific activity been seen on any subject. Numerous experiments have been carried out, and are still being pursued with renewed enthusiasm and vigour, which give us the hope that we may soon be able to check the ravages of a disease which has for so long baffled the united efforts of hygienists and legislators in every civilized country during the last 400 years.

While we are waiting for the ideal prophylaxis, viz., an anti-syphilitic vaccine, the discovery of Professors Metchnikoff and Roux, that calomel ointment can prevent the onset of the disease, places at our disposal a simple and easy method of combating it, which deserves to be thoroughly tried.

The full details of the experiments on which the above discovery is based, will be found in this thesis.

Any one can judge for himself of the scientific accuracy and care with which they have been carried out.

The Under-Secretary of State for War in France has just issued a circular with regard to the prophylaxis of venereal diseases in the army. Amongst other measures, he orders the issue to all the men of calomel ointment, which is to be served out in small wooden boxes containing 5 grams of ointment. It is hoped that sufficient material will have been collected at the end of June to permit of the publication of comparative statistics on the value of the measure. Special notes are to be made of the cases occurring in soldiers who have carried out this prophylactic treatment.

I have been trying on a small scale the utility of the ointment, but do not possess as yet sufficient data to enable me to express an opinion on its practical value.

In an appendix (Ap. III.) I have given a *résumé* of the attempts that have been made to obtain an antisymphilitic vaccine.

Jan. 10th, 1908.

F. L. DE VERTEUIL.



## PROPHYLAXIS OF SYPHILIS.

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### *CHAPTER I.*

#### **SYPHILITIC CONTAGION.**

IT has been known for quite a long time that syphilis is contagious; but the knowledge of the precise nature of the laws which govern this contagion has only been acquired recently.

Experiments made on monkeys, and the discovery of the spirillum, have scientifically confirmed data gleaned merely from clinical experience; we are now aware of the fact that certain conditions are requisite before a healthy individual can contract syphilis.

I. The person who transmits the disease must of necessity be suffering from a specific lesion, or from some ordinary lesion which may serve as the channel of exit through which the virus is to come in contact with the healthy organs.

II. The healthy individual, on the other hand, will never be contaminated if his skin and mucous membranes are intact.

III. The syphilitic virus, in order to produce an infection, must possess certain qualities.

We propose to study in this chapter the respective parts played by each of these three factors in the contagion of syphilis.

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#### I.—LESION IN THE TRANSMITTER (“ SYPHILISATEUR ”).

1. **The Results of Clinical Experience.**—The virus of syphilis, whatever the mode of contagion, always comes from an individual previously infected.

To become capable of transmitting the disease, the individual must present some solution of continuity at some spot of his integuments. This solution of continuity might only be a scratch, or some small bleeding wound ; in most cases it will prove to be one of the many cutaneous or mucous lesions which are met with at the different periods of syphilis.

**Chancre.**—By comparing the copy with the original, clinical observation has definitely proved that the chancre is contagious.

Bassereau, Clerc, and especially Fournier, have shown that individuals suffering from chancres and subsequent constitutional symptoms, have invariably had the disease communicated to them by some one affected with a chancre or constitutional lesion.

Moreover, experiments have long since confirmed the truth of this proposition.

Rinecker, Rollet, Gibert, the anonymous writer of the Palatinate, Danielssen, Belhomme, Lindwurm, Puche, to quote only the names of the chief experimenters of the last century, all obtained successful results by inoculating the products of the chancre into healthy individuals.

**Mucous Patches.**—It is now established that the mucous patch is one of the most common causes of infection. This opinion seemed at first entirely opposed to the results obtained experimentally by Hunter and Ricord. But their observations are rendered valueless because of the erroneous ideas they entertained concerning the period of incubation.

Wallace in 1835, Colles in 1844, Auzias Turenne in 1855, Langlebert and Rollet in 1856, and especially Fournier,<sup>1</sup> accumulated facts proving the transmission of syphilis by secondary lesions, and were finally so successful that Ricord himself had to bow to their arguments (31 May, 1859).

**Tertiary Lesions.**—It is but a short time ago that the non-contagious nature of tertiary lesions was almost universally accepted.

A few extremely rare inoculations on the human subject helped to confirm this opinion. Tanturri, of

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<sup>1</sup> Fournier, *The Late Contagious Nature of Secondary Lesions*.

Naples, in 1865, had inoculated without success into a healthy woman the products of a large subcutaneous gumma. In 1871, Profeta performed an inoculation, with negative results, with secretion derived from a syphilitic tubercle. Diday was equally unsuccessful with pus taken from a gumma.

During the last few years, however, practitioners have observed clinical facts tending to throw much doubt on the results of these rare experiments.

Landouzy reported to the Dermatological Congress of Paris, in 1889, two cases of syphilitic infection in the tertiary period. One of these patients was a man suffering from a gumma of the penis, who transmitted the disease to his wife.

As a result of this communication, Fournier stated that he had seen a similar case.

Mauriac and Feulard, in 1896, have reported cases of infection from gumma, tertiary glossitis, and tertiary chancriform syphilide.

**Blood.**—The fact that blood from a syphilitic individual can produce the disease was experimentally demonstrated, in spite of the failure of Thiry and Laglade to do so. Few are ignorant of the famous experiments of the anonymous writer of the Palatinate, in 1855, and especially that of Professor Pellizari, in Florence, in 1860; the latter inoculated three of his assistants with blood from a syphilitic patient. Only one of them contracted the disease,



viz. Dr. Bargioni, who was inoculated with the most freshly drawn blood.

Waller in 1850, Gibert in 1859, Lindwurm in 1861, obtained similar results.

In accordance with experimental research, Mauriac states that he has seen the disease undoubtedly transmitted from a simple bleeding fissure in a patient who had contracted the disease four months previously.

The experiment of Diday on syphilitic vaccination, in 1848, seems to prove that the blood does not retain its virulence in the tertiary period.

Opinion has been very much divided, especially in former days, as to the contagious nature of the sperm, saliva, tears, sweat, and milk.

The vast majority of authors do not at present admit that the disease can be thus conveyed. Although a few cases, apparently due to the saliva, have been recorded, this is probably owing to the fact that the individuals suffered at the time from mucous patches, or from some erosion which allowed the virus to come through the mucous tissues.

The same explanation will probably help to elucidate those cases, more or less truthfully recorded, of infection due to the tears, the sweat, and the lacteal secretion.

## 2. Contribution of Experimental Syphilis to the

**Results of Clinical Experience.**—The discovery of the relative receptivity of the inferior catarrhini, and especially the absolute receptivity of the anthropoid apes, has so revolutionized the study of syphilis that experiments, naturally impossible on man, can now be freely carried out.

Every kind of syphilitic lesion has been inoculated into monkeys by experimenters, of whose results we shall now make a critical survey.

**Chancre.**—The first experiment of Metchnikoff and Roux was carried out on a female chimpanzee, which was inoculated with some serous exudate taken from an indurated chancre in a man. Twenty-six days after the introduction of the virus, there appeared at the site of inoculation a small transparent vesicle surrounded by a red zone, which did not show a clear line of demarcation from the adjoining tissues. This vesicle soon gave place to an erosion, which gradually became more and more indurated, and at the same time there was a distinct enlargement of the lymphatic glands in both groins.

Twenty days after the appearance of the initial vesicle on the prepuce, Metchnikoff and Roux exhibited their chimpanzee to the Academy of Medicine<sup>1</sup> in order that the members of this assembly could verify the result of this first experiment. All the members present who examined the

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<sup>1</sup> *Bulletin de l'Académie de Médecine*, 28 July, 1903.

animal were satisfied as to the syphilitic character of the lesion, and the specialists, amongst whom we may mention Professor Fournier, Messrs. de Castel, Hallopeau, and Marc Sée, diagnosed an indurated chancre.

We have spoken somewhat in detail of this experiment, because it was the first of that fine series of researches on experimental syphilis carried out at the Pasteur Institute by Metchnikoff and Roux.

Since then the inoculation of the indurated chancre has been repeated hundreds of times on the anthropoid apes, as well as on the inferior catarrhini; and the fact that the primary lesion is contagious has been clearly and definitely shown.

**Secondary Lesions.**—In November, 1904, Metchnikoff and Roux<sup>1</sup> obtained positive inoculations on the chimpanzee with the products of secondary lesions, viz., mucous patch and chancriform syphilis.

In June, 1905, Thibierge and Ravaut<sup>2</sup> published the results of a series of researches on the syphilis of the lower apes (*Macacus*). They also obtained positive results by inoculating the products of mucous patches into the free border of the eyelids of these animals.

Analogous experiments were repeated in Germany

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<sup>1</sup> Metchnikoff and Roux, "Experimental Syphilis," *Ann. de l'Inst. Past.*, 1904.

<sup>2</sup> *Bulletin de la Société Médicale des Hôpitaux*, June, 1905.<sup>1</sup>

with success, which proved conclusively the truth of the general opinion held by clinicians concerning the contagious nature of secondary lesions.

**Tertiary Lesions.**—"In our experiments, the primary and secondary lesions of man and of monkeys have been shown to be inoculable," says Metchnikoff,<sup>1</sup> "but although we made several attempts to inoculate gummata, these did not yield any positive results. On the other hand, Finger and Landsteiner, as well as Neisser, Baermann, and Halberstätter have, in five cases, succeeded in producing an indurated chancre in monkeys inoculated with products taken from the periphery of gummata."

In his communication to the Congress of Lisbon, Prof. Neisser<sup>2</sup> made the following statement: "The contagious nature of all syphilitic products, primary, secondary, as well as tertiary, has been demonstrated, but the last are only contagious when the tertiary neoplasm is not in a state of degeneration or of suppuration.

"We may state that all ulcerated and soft gummata no longer contain any inoculable virus. Finger and myself succeeded in obtaining positive inoculations, because we had at our disposal gummata that had not yet undergone any necrotic transformation, and were still covered with healthy skin."

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<sup>1</sup> In *Report on Experimental Syphilis at Congress of Lisbon*, 1906.

<sup>2</sup> Neisser, *Communication at the Congress of Lisbon*, 1906.

These different experiments prove definitely that tertiary lesions are sometimes inoculable.

“As for the *blood*,” says Neisser in the same report, “new experiments made on monkeys have confirmed the results obtained by the ancient writers on syphilis as regards man.” Hoffmann<sup>1</sup> has also successfully inoculated into monkeys blood from syphilitic patients. With the *serum* Finger once succeeded in obtaining a positive inoculation. Neisser repeated the experiment five times, but failed.

**Hereditary Syphilis.**—“On three occasions,” the Professor of Breslau added, “I have been able to testify to the infectious nature of all the organs. In the first case, I obtained chancres in all the monkeys I inoculated with every one of the different organs I had examined, viz., lungs, liver, spleen, kidneys, suprarenal capsules, and testicles; in the second case, with the blood of the heart, and the ovary; and in the third case, with the purulent mucus from the nose. This last experiment brings to light the fact that a child may prove contagious to those in immediate contact with it.”

#### CONCLUSIONS.

I. *Clinical observations, experiments on man, and more recently, inoculations of certain species of simian*

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<sup>1</sup> *Deutsche medizinische Wochenschrift*, 1906, No. 13.

*apes, prove that the lesions of primary, secondary, and tertiary syphilis contain an infectious virus.*

*2. Gummata solely, at least experimentally, are rarely the starting-point of a syphilitic infection.*

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## II.—LESION IN THE PERSON WHO CONTRACTS THE DISEASE ("SYPHILISÉ").

### I. Is it possible to Contract Syphilis through the Intact Skin or Mucous Membrane?

This very important point was formerly a much-debated question. At the present moment every one is unanimous that a loss of continuity in the cutaneous or mucous integuments is requisite before the virus can penetrate into the organism.

As Ricord observes in his *Lettres sur la Syphilis* (p. 151), "The observation and analysis of facts prove that the contagious nature of syphilis, whatever be the mode of inoculation, is in the end a process of inoculation more or less analogous to that produced by the lancet." This is a clear and definite statement, to which all those who have made a special study of syphilis since the time of Ricord have agreed.

It is no longer believed that an epithelium physiologically intact, but congested at certain physiological moments, can allow the virus to filter through. This would be even more difficult through the skin, "the natural barrier to microbic invasion."

The depressions in which the hair follicles and sebaceous glands are situated offer a channel of entry to the microbes of the skin, and are easily penetrated by streptococci and staphylococci. These orifices, however, do not seem "in their normal condition to be able to serve as a port of entry to the virus" (Neisser).

It follows that syphilitic virus can be applied to the skin or normal mucous tissue without infecting the organism.

We have daily proof of this: there are men who have venereal intercourse with highly-infected women, and who do not contract the disease; there are medical men who constantly examine contagious lesions, and yet escape infection.

This first proposition, viz., the necessity for a solution of continuity, is of the greatest importance. It explains why the regions which are the most liable to abrasions are those that are usually infected. It explains how it has been possible for men and women, in rare instances, to transmit the disease without ever having been contaminated themselves; and, lastly, it throws some light on the presence of multiple chancres under certain conditions.

2. **Must the Lesions be Deep?**—In other words, at what depth, and in which of the different layers of the integument, does the inoculation take

place? We can locate this anatomical point, and show that syphilis is a disease due to a dermal, and not to an intra-epidermal inoculation, as has often been stated.

Clinically, it is known that the virus may be grafted on a slight excoriation, which may be imperceptible to the naked eye.

It might be deduced from this, that it is not necessary for the virus to penetrate to the dermis.

However, at present, it is from experiments that we shall obtain the most reliable information. On investigating the successful inoculations practised, formerly on man and now on monkeys, we find that some experimenters exposed the dermis by means of a blister, whilst others inoculated the pus into the dermis by means of a bistoury or by scarification.

A good scarification must penetrate to the dermis, which, perhaps, explains why Neisser,<sup>1</sup> who for a long time only carried out superficial abrasions, at first denied the possibility of infecting the lower apes with syphilis.

Finger and Landsteiner introduced the virus into small pockets, produced in the dermis by means of a cutting instrument.

Metchnikoff,<sup>2</sup> by utilizing this method, consider-

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<sup>1</sup> *Deutsche medizinische Wochenschrift*, 1904, No. 1422.

<sup>2</sup> *Report at the Congress of Lisbon*, 1906.



ably diminished the percentage of the lower apes that failed to contract the disease.

Moreover, on every occasion on which we have seen Metchnikoff practising syphilitic inoculations, whether by Finger's method or by scarification, there was always a slight flow of blood. In all these cases, the inoculation was done through the epidermis, and reached the Malpighian layer.

"The study of the initial stage of the papule ("Initial Stage of the Syphiloma," Dr. Paul Salmon, in *Transactions, Société de Biologie*, p. 9, 1905) which has been excised by the knife, shows that syphilis causes a marked inflammation of the dermis, with an accessory inflammation of the epidermis.

"In the dermis, the syphiloma develops both on the surface and in the deep layers. Superficially, the cellular subpapillary layer becomes infiltrated with mononuclear cells of two kinds, one of which is stained dark by aniline dyes, while the other takes on a lighter stain; it is in this layer that the syphiloma starts. The instrument of inoculation penetrates into, and brings the syphilitic virus in contact with, this region, which is next to the epidermis, and it is at this spot that the parasite of syphilis will develop."

*The following is now an established fact:* To communicate the disease by inoculation of syphilitic pus, the pus must go through the epidermis, and come

in contact with the dermis. This enables us to explain without difficulty the mode of production of the chancre : at the time of coitus, an abrasion is produced (which is a matter of frequent occurrence), or else a former affection (eruption of herpes, soft chancre, balanitis, etc.) exposes the dermis, and so enables the virus to come in contact with it.

From the study of the above, another question naturally presents itself for investigation. We know that the syphilitic virus communicates syphilis when it comes into contact with the dermis. Would the same thing happen were the virus introduced more deeply into the organism ; that is, if the inoculation, instead of being intradermic, was hypodermic ? The solution of this problem is the more interesting, because on its solution there also hinges that of certain cases of so-called spontaneous syphilis, syphilis without a primary chancre, the existence of which is entirely denied in the present day by almost all writers on syphilis, Fournier, Gaucher, etc., but which was formerly maintained by different authors.

Experiment gives us a definite answer. "It is impossible to infect monkeys by a subcutaneous injection of the virus. The animals are neither infected, nor immunized, for in all these cases they can be reinoculated successfully."<sup>1</sup>

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<sup>1</sup> Neisser, Congress of Lisbon, 1906.

In order, then, to perform a successful inoculation, *we should not penetrate beyond the dermis.*

To resume: clinical study, both experimental and histological, of the acquired or inoculated chancre, proves plainly that *one condition is necessary and sufficient* for the syphilitic virus to produce a chancre: this is *the introduction of the virus into the superficial layers of the dermis.* The importance of these facts can easily be estimated when we investigate the means whereby we can reach the syphilitic virus before it has time to invade the organism.

As it is always essential that the virus should go through the dermis before infecting the organism, we naturally should investigate whether there exists a therapeutical agent, physical or chemical, which would reach the virus in the dermis.

## CONCLUSIONS.

1. *It is impossible to contract syphilis without a lesion.*

2. *This lesion, which serves as the port of entry, must be dermo-epidermal.*

3. *As this lesion is very superficial, we could probably reach the syphilitic virus localized in the lesion by using a therapeutical agent capable of penetrating to the dermis.*

## III.—THE VIRUS.

Since the advent of microbiology, there has been hardly a year in which the announcement of the discovery of the microbe of syphilis has not been made.

We shall not enter into the history of the question, since, according to the most reliable bacteriologists, *the true pathogenic agent of syphilis has at last been discovered*. It is a mobile organism, in the form of a very fine spiral, discovered by Schaudinn in human syphilitic products and since further studied by himself and Hoffmann.<sup>1</sup>

The *Spirochæta pallida* has not up to the present been cultivated. Levaditi,<sup>2</sup> of the Pasteur Institute, has, however, advanced one step in this direction. Though he has not succeeded in cultivating the spirillum of syphilis, he has been successful with two analogous spirilla—that of septicæmia of fowls, and that of recurrent fever.

It will, however, probably require some advance in bacteriological methods before a reliable practical method of culture of the *Spirochæta pallida* on a large scale will prove successful.<sup>3</sup> There are still a

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<sup>1</sup> *Arbeiten a. d. k. Gesundheitsamte*, 1905, vol. xxii. p. 527, and *Deutsche medizinische Wochenschrift*, 1904, No. 15.

<sup>2</sup> *Bulletin de l'Académie des Sciences*, May, 1906.

<sup>3</sup> Levaditi and M'Intosh (*Anns. de l'Inst. Past.*, Oct. 1907) state that they have succeeded in cultivating the *Spirochæta* by means of collodion sacs placed in the peritoneal cavity of *M. cynomolgus* and subsequently of rabbits. When tested on monkeys and a chimpanzee, the parasite was, however, found to have completely lost its virulence.

few authorities who decline to accept its specific nature until this has been achieved.

The study of the researches which have been carried out as to the existence of the spirochæte in the various human syphilitic lesions, and their special distribution in the interior of these lesions, has not only enlightened us on their etiological relation to the disease, but has given us information of the greatest interest as regards the method of communication of the disease.

It is unnecessary to give the names of those who have found the pale spirillum in the primary, secondary, or tertiary lesions, for all who have searched for it have been successful. The fact that it has been found by every observer, even in the most distant countries, is an excellent argument in favour of the specific nature of the organism.

Another interesting fact is that it has been found, according to Metchnikoff and Roux,<sup>1</sup> and subsequently Neisser, Finger, and others, in the lesions of experimental syphilis of the monkey.

Shortly after their first communication on the *Spirochæta pallida*, Schaudinn and Hoffman<sup>2</sup> discovered its presence in the lymphatic glands.

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<sup>1</sup> Metchnikoff and Roux, Microbiological Researches on Syphilis, *Bulletin de l'Académie de Médecine*, May, 1905, p. 468.

<sup>2</sup> Schaudinn and Hoffmann, *Deutsche medizinische Wochenschrift*, May, 1905, pp. 711-714.

## 18      Prophylaxis of Syphilis

Queyrat and Levaditi,<sup>1</sup> by means of sections, which we shall treat of later, were equally successful in finding it in every third case examined.

Several observers, notably Noeggerath and Stahelin, have found the syphilitic spirillum present in the blood, especially at the secondary period, when the disease was generalized.

In spite of the most ingenious experiments and of the perseverance of the investigators, no one had been able to find the spirochæte in tertiary syphilis, and many were the conjectures to explain its absence, or at least its invisibility, when Schaudinn (in the discussion which followed the communication of Professor Neisser at the Congress of Lisbon) stated that he had succeeded in finding a mass of five to six spirochætes at the periphery of a gumma of the liver.

To sum up: in all manifestations of syphilis, whether acquired or experimental, it has been possible to find the spirillum. One more problem yet remained to be settled. Would it also be found in hereditary syphilis?

This obviously interesting question excited the curiosity of bacteriologists in France as well as in Germany, as a result of which the problem was soon settled.

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<sup>1</sup>Queyrat and Levaditi, *Société Médicale des Hôpitaux*, 5 April, 1906.

Buschke and Fischer,<sup>1</sup> on the 18th May, 1905, found the spirillum in the blood and viscera of a child who had died eight weeks after birth, whilst suffering from symptoms of hereditary syphilis. On the 20th May, Levaditi and Salmon,<sup>2</sup> in two cases of syphilitic palmar and plantar pemphigus, found in the fluid of the bullæ, and especially in the scrapings from the floor of the lesions, spirilla similar to those described by Schaudinn.

Queyrat, Levaditi, and Feuillé,<sup>3</sup> made sections from the liver and the spleen of a macerated fœtus, in which they found spirilla in abundance.

These results have since been confirmed by numerous observers, and the presence of the spirochæte in the organs of hereditary syphilis is no longer disputed.

This fact, coupled with the presence of the microbe in experimental syphilis, constitutes one of the most convincing arguments that can be advanced in support of its specific nature.

We owe to the methods of staining, and to the many works of Bertarelli and Volpino, as well as those of Levaditi in connection with Manouélian,

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<sup>1</sup> *Deutsche medizinische Wochenschrift*, 18 May, 1905, and 25 May, p. 839.

<sup>2</sup> *Société de Biologie*, May, 1905.

<sup>3</sup> Queyrat, Levaditi, and Feuillé, *Société Dermatologie et Syphiligraphie*, 1905.

Queyrat, and Feuillé, our knowledge of certain curious facts concerning the distribution of the spirillum in syphilitic lesions.

By means of sections, they have been able to note the following in the chancre: As a rule, the spirilla are not present on the surface of the ulceration, on which, on the contrary, there are a large number of microbes of secondary infection, especially cocci, which do not penetrate any deeper. The parasites, on the other hand, are numerous on that zone of the epidermis which is in the immediate neighbourhood of the ulceration.

In a previous work we read the following equally interesting conclusion: "The *Spirochæta pallida* proliferates between the epidermal cells of the deep layer, in the immediate neighbourhood of the primary and secondary lesions. In the secondary lesions, the histological lesions and the distribution of the treponemas are exactly similar to what we have described in the primary lesion."

We have learnt that the spirochæte of Schaudinn, which is rare on the surface of ulcerated lesions, is found in abundance in the deeper layers.

This fact is all the more interesting because experiments on monkeys have shown that a *large quantity of virus* was required in order to obtain positive inoculations. Experiments have shown that the quantity of virus is a factor of equal importance to



the rapidity of inoculation, as well as the age and nature of the syphilitic product employed.

Neisser is even more emphatic, and declares<sup>1</sup> that it is the number of spirochætes inoculated, and not the quality of their virulence, which exerts a more or less rapid influence on the onset of the primary lesion.

If we accept the truth of this, we shall easily understand, by the knowledge gained from sections concerning the distribution of the spirilla, the part which sexual intercourse plays in contagion; as a result of repeated friction, the surface of the lesion is rubbed off, the underlying layer laid bare, and the spirilla are set at liberty.

It can then be easily understood why in certain cases where connection has been rapidly effected with contagious individuals the disease is not transmitted, for the time was too short to permit of the liberation of a sufficient number of spirilla.

## CONCLUSIONS.

1. *The spirochæte, the pathogenic agent of syphilis, is found in all the different lesions: chancre, papule, mucous patch, pemphigus, tubercle, and even gumma. The organism is found in hereditary syphilis, as well as in the acquired disease.*

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<sup>1</sup> Congress of Lisbon, 1906.

2. *On the one hand, search for the spirilla in scrapings, and especially in sections, shows that the microbes are less abundant at the surface than in the depths of the lesion.*

3. *On the other hand, experiments prove the part played by the factor "quantity" in the inoculation of the spirilla of syphilis.*

4. *This explains why syphilis is propagated chiefly as the result of prolonged sexual intercourse, and why extra-genital syphilis is relatively uncommon.*

*CHAPTER II.***THE GENERALIZATION OF THE VIRUS.**

WE have studied the conditions necessary for the transference of the microbe of syphilis from one human being to another.

We know how the spirillum obtains entrance into the lesion of a healthy organism; this constitutes the first stage of the infection, during which syphilis is a local disease.

The second stage will be inaugurated by the passage of the virus from the sore into the system.

As soon as this is accomplished, the healthy individual becomes syphilitic, and the disease is generalized, or becomes "constitutional," according to the term employed by the ancient writers on syphilis. It is evident that the important point for us, is to find out exactly when this generalization takes place; for as long as syphilis is a local cutaneous lesion, it is accessible. When the virus, however, has got into the blood—a popular expression, which is strictly accurate—it is no longer within reach.

Syphilis, according to some observers, only reaches the blood at a later stage. They state that the

*chancre* itself is at first a *local lesion*, which precedes the general infection ; this opinion, defended formerly by Jean de Vigo from 1514, was maintained afresh by Auspitz, of Venice, about 1877. Along with Unna, Reiss, and Blosckho, he advocated and—as a logical sequence—practised the excision of the chancre.

The opposite was contended by others, who declared that syphilis became generalized long before the appearance of the chancre.

As soon as the chancre has appeared, it is too late to stop the spread of the disease, even though the chancre is immediately excised. Though the statistics of Crivelli and D'Ehlers show one success in every four excisions, in those cases they either had to deal with simple chancre, or they did not follow the course of the disease long enough after the operation. Moreover, at the Congress of Copenhagen, in 1884, several very careful observations were reported, showing the inefficacy of this operation.

Martineau mentions a case of Rasoir's, and Lelior a case of his own, in which, though excision had been done twelve hours after the appearance of the chancre, the onset of the disease was in no way arrested.

Dr. Barthélemy quoted a case in which Professor Fournier had been able to excise the chancre even at an earlier period, but without success.

This method had its origin in a false conception,

and it gradually ceased even to be spoken of. However, all these theories have recently been brought forward again as the result of the successful experimental re-inoculation of the chancre.

Queyrat has made several communications on the subject; he has been able to exhibit syphilitic individuals, in whom he had succeeded in reproducing syphilomata by inoculating them with virus from their own chancres.

A pupil of Professor Gaucher, Sabaréanu, has treated the whole question in his thesis *On Successive Syphilitic Chancres*.

Experimental inoculation on monkeys, in accordance with clinical facts, proves that the chancre does not appear until syphilis has already become a generalized infection, and, on the other hand, it is possible to act on the point of entry of the virus for a brief period after the inoculation; thus, Metchnikoff and Roux have arrested the development of syphilis in one case twenty-four hours after inoculation, by excising the spot where the virus had been injected. Neisser, however, declares that he has not been successful, although he employed the same method only eight hours after inoculation.

In another series of experiments, which we shall describe *in extenso*, Metchnikoff and Roux, by making use of a different method, have successfully combated the lesion eighteen hours after injection;

in a second case, however, in which they had employed their method twenty hours after, they obtained a negative result.

#### CONCLUSIONS.

*We must act very quickly if we desire to exert any preventive influence on the point of penetration of the virus ; for syphilis is a disease which soon becomes generalized.*

## CHAPTER III.

## ACTION OF PHYSICAL AND CHEMICAL AGENTS ON THE SYPHILITIC VIRUS.

## I.—PHYSICAL AGENTS.

EXPERIMENTS have enabled us to prove what clinical facts seemed to render probable.

“The syphilitic virus,” says Metchnikoff, “is very frail. It can live but for a few hours outside the organism; drying destroys its virulence (Salmon).<sup>1</sup> When kept at a low temperature it soon ceases to be active. In one of our experiments with M. Roux, we inoculated into a papion a large amount of virus from a child suffering from pemphigus, which had been previously kept for three days in an ice-chamber at 10° C. This virus had no effect, nor did that derived from the liver of a still-born syphilitic child, which had been preserved under the same conditions.

“Heated to 48° and 51° C., the virus no longer transmits syphilis.”

The feeble resistance of the micro-organism to

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<sup>1</sup> *Société de Biologie*, 1904.

desiccation throws a new light on the question of extra-genital syphilis; to communicate the disease the virus must be fresh; it follows then that intermediate contagion must only rarely be the means of propagating the disease, and in future, cases of infection of this kind should be verified by careful enquiry before being accepted as authentic.

The knowledge of this fact will also prove valuable when we come to study the question of the prophylaxis of syphilis. It is evident that the best remedy against extra-venereal syphilis is the observance of the most elementary laws of hygiene, and the suppression of certain customs, especially the buccobuccal kiss cherished by the Russians. Though reliable statistics prove that extra-genital syphilis may be easily combated, no efficacious method has been found, up to the present, to prevent infection by means of venereal intercourse; our recently-acquired knowledge of the small powers of resistance of the virus gives us, however, the hope that we may yet attain this end by methods much more simple than were, until lately, thought possible.

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## II.—CHEMICAL AGENTS.

**Mercury.**—The virus, *in vitro*, mixed with glycerin, will not lose its virulence. “Glycerin, added to the



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syphilitic virus, does not destroy its pathogenic action.”<sup>1</sup>

In medical practice two substances are employed in syphilis—iodide of potassium and mercury. Iodide of potassium was first used by Wallace. Recent works on this drug and the iodides show the influence it exercises on the circulation and on the migratory cells; so that, as we should expect, iodide of potassium is found to be a very useful drug against the sclerotic changes of tertiary syphilis. It is, however, a matter of common knowledge that it has no influence on the chancre and on secondary lesions; it has never been considered as an antimicrobial agent. We must not, therefore, expect to find in this drug an antidote against the poison of syphilis.

Therapeutics boasts that it possesses in its armoury two or three specific drugs, amongst which mercury is considered to be the most certain and efficacious in its action.

Syphilis made its appearance in Europe in 1494; and as early as 1495 Marcellus Cumanus recommended the use of a mercurial ointment (Hallopeau, *Thèse d'Agrégation*, 78). His example was followed by Vigo and Bérenger of Carpi.

Mercury was only administered internally towards

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<sup>1</sup> Metchnikoff and Roux, *Annales de l'Institut Pasteur*, Nov. 1904.

the year 1535 by Pierre-André Mathiole, who prescribed the red precipitate; pure mercury was employed subsequently, and entered into the composition of the famous pills of Barberoussa; later, with the advent of chemical discoveries, came the different preparations which are now more or less in use.

“ *Does mercury possess a curative action on the symptoms of syphilis?* ”

“ It has been said that this is an illusion, and that the effect of time and the morbid evolution of the disease account for the good which is ascribed to the use of mercury. Syphilitic symptoms are not continuous, permanent, and eternal; they terminate in a natural cure, *sponte suâ*, in which the concurrent use of mercury plays no effective part. This may certainly be so; there are syphilitic lesions which can be cured without treatment; of this there is not the least shadow of a doubt. Are all the lesions, however, of syphilis cured in this way? Are those numerous lesions which terminate in sclerosis, mutilation or destruction of tissues, cured in this way? Are all those whose lesions bring them to our operating theatres cured in this way? ” (A. Fournier).<sup>1</sup>

The objection has been raised against mercury,

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<sup>1</sup> *Treatment of Syphilis.*

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that even when administered early, it does not prevent the advent of secondary and tertiary lesions.

To this Fournier replies that he does not pretend that he can immediately eradicate syphilis in such a manner that it will no longer show signs of activity. "We hold," he says, "just the opposite opinion. If we do influence the course of and attenuate the disease, we only obtain this beneficial result slowly, gradually, and progressively; we are of opinion that if we are finally able to overcome its diathesis, we only succeed in doing so by long and continued treatment, spread out over the course of several years."

In order to convince those who are still in doubt on the subject, he gives the following statistics and analysis of 1703 cases of tertiary lesions :—

Of these, 59 occurred after, and in spite of, most careful treatment, which one would imagine to have been quite sufficient; while 1644 followed either irregular and totally inadequate treatment, or complete absence of treatment.

Fournier adds, "In presence of the above results, commentary would be superfluous."

This, then, according to the best known modern authority on the disease, is the action of mercury on syphilis.

If we take into account the quantity of mercury administered, which is infinitesimal and quite insignificant in comparison with the weight of the body

(1 centigram of mercury represents the average daily dose, which repeated five to six times often suffices to disperse commencing lesions), we can only explain the effects produced as being due to the small powers of resistance of the virus demonstrated by experiments *in vitro*.

The question has been asked, *How does mercury act* when thus employed as a general drug for syphilis? How does it act when administered by the mouth, or by subcutaneous injections? Does it act locally against the chancres, mucous patches, and the other lesions of syphilis—"chronic recurrent syphilis," as Roux and Metchnikoff have named it?

The aid of histology and cytology has been requisitioned, in order to obtain definite information on this point.

By excising syphilides from time to time from a patient who is undergoing mercurial treatment, we have been able to follow step by step cellular reactions and leucocytosis, and can diagnose almost with certainty in a histological section the mercurial cure of a syphilide.

Justus, who has studied the action of mercury in syphilis by means of the reaction produced by sulphuretted hydrogen, has found the mercury apparently attracted by the cells of the syphilitic infiltration.

The cytological examination of the blood in the

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course of syphilis gives very variable results. According to some authors, hæmatological researches would not seem to favour the use of mercury. "There does not seem to be any favourable influence after the absorption of mercury" (Oppenheim and Lowenbach). "Its use does not prevent the appearance of syphilitic anæmia" (Colombini and Simonelli).

Other histologists, on the other hand, state that there is a distinct improvement in the condition of the blood which has been impoverished by the syphilitic infection, and have confirmed the reaction of Justus. They state that under the influence of treatment there is a sudden decrease in the hæmoglobin of the blood, followed by a rapid rise. This phenomenon does not occur in a healthy individual, and is confined to the syphilitic.

It has been stated, and this is quite in accordance with the reaction of Justus, that the mercurial poison is better borne by a syphilitic than by a normal individual.

Whatever be the truth, it seems proved at all events that mercury acts in a mild way as an anti-parasitic agent, and is absorbed by the whole system only through the intermediary of the cells of the organism.

We can compare this action to that of a small dose of antidiphtheritic serum which is incapable of

neutralizing the toxin or of destroying the diphtheria bacillus.

Experiments on monkeys, and the discovery of the spirillum, will, no doubt, enable us to arrive at the truth. Even at the present moment they enable us to confirm certain hypotheses formerly advanced on the prophylactic action of mercury.

The constant use of mercury, in view of its general action, *does not prevent the onset of syphilis*, as is proved by the fact that men who work in mercury mines contract the chancre, those who are accidentally poisoned by mercury may have syphilis, and that there are "men who have contracted the disease immediately after having followed a complete course of mercurial treatment." Neisser, from his experiments on monkeys, has arrived at analogous conclusions :—

" 1. The evolution of the chancre is the same in a mercurialized individual as in one who has never had mercury. We began injections on the same day as the inoculation: yet in spite of this the indurated chancre developed without any modification in its period of incubation.

" 2. The infection becomes generalized in the same way in mercurialized animals as in those which are not. In fact, in spite of this early treatment, we can show that the poison is still virulent by

inoculation of the spleen and bone-marrow into other monkeys."

Finger and Neisser have also shown that monkeys can be inoculated with recent gummata. We are aware of the fact, from the confession of Fournier himself, that mercurial treatment carefully carried out does not always prevent tertiary symptoms. From this we are bound to conclude that the spirochætes are not destroyed, since the organism, after years of treatment, still contains virulent products.

Must we gather from this that the beneficial effects of mercury have been exaggerated, and that it has no action on the syphilitic spirillum?

"I am, on the contrary, quite convinced," says Neisser, "that it is precisely those experiments now engaging our attention which prove that it is only the continued intermittent treatment by mercury which enables us to attain our end, viz., a radical and definite extinction of the spirochætes, without leaving any form of latent infection in the organism."

*The use of mercury applied locally in syphilis* has been advocated by eminent authorities on syphilis, such as Diday, and more recently by Fournier.

Hallopeau especially, in numerous works on the subject, has striven to show the advantage of the method, and only quite lately made the following

remarks (Society of Dermatology and Syphiligraphy, May, 1906) :—

“ I systematically employ this local treatment in every syphilitic lesion accessible to its influence. Thus, in cases of indurated chancre, I employ calomel ointment, or cotton-wool impregnated with sublimate (1-5000) ; I advocate the same treatment in cases of mucous patches, or if they are limited to the tongue, cauterization by the acid nitrate of mercury, using the necessary precautions ; in cases of serpiginous syphilides, either the emplastrum of Vigo<sup>1</sup> or of Vidal,<sup>2</sup> or one of the methods indicated above ; in cases of ocular syphilis, a collyrium, containing sublimate of mercury ; in generalized syphilis, baths of sublimate ; in specific ozæna, spraying with a solution of sublimate ; in affections of the digestive tube or the liver, calomel. In addition to the specific treatment, I use nitrate of silver in cases of ulcerated mucous patches or vegetating tubercles, on the surface of which there is an associated infection. Unless I am mistaken, this systematic use of local mercurial treatment, which I have already advocated on several occasions, should

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<sup>1</sup> The emplastrum of Vigo is a very old preparation, containing a large variety of ingredients, of which mercury is the principal.

<sup>2</sup> Emplastrum of Vidal: cinnabar is the active ingredient of this preparation.



not be looked upon as being of little importance; I personally consider it to be of great practical value."

This eminent authority has based his opinion on a long and varied experience.

It is curious to note how the efficacy of this practice is confirmed by the search for the spirillum. "Among sixteen cases of chancre," says Bodin,<sup>1</sup> "the presence of the *Spirochæta pallida* was detected ten times; whilst negative results were obtained in six cases, three of which had been treated with calomel ointment for several days, while the remaining three were non-treated chancres of two months' duration on the point of healing."

Though the preventive influence of mercury as regards syphilis is feeble and practically nil, an unbiassed study of the effects of this drug shows that it exercises in most cases an undoubted and marvellous curative action. In no other infectious disease has the use of such small quantities of a chemical substance given such satisfactory results.

### CONCLUSIONS.

1. *Mercury has an undoubted influence on syphilis, and should in sufficient doses destroy the spirochæte.*

2. *When we consider, from our previous knowledge, that the syphilitic virus never penetrates through a*

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<sup>1</sup> *Annales de Dermatologie et Syphiligraphie*, 1905, p. 984.

*healthy intact skin or mucous membrane, and that to infect the organism it must be deposited in the superficial layers of the dermis, and not beyond it, there is no reason why an agent so definitely antisyphilitic as mercury should not be capable of reaching and destroying the pale spirochæte, as long as this latter is on the surface, where we know that it remains for some time before penetrating into the deeper layers.*

## CHAPTER IV.

PROPHYLAXIS OF SYPHILIS BY  
CHEMICAL AGENTS.

I N the study of syphilis we have only recently acquired a sound knowledge of certain points which will be of help to us when we consider the question of prophylaxis.

Although our knowledge of the disease was formerly less precise, the chief factors had, nevertheless, already been established. It has been known since the beginning of the sixteenth century that syphilis is only contracted by contagion, which is in most cases due to sexual intercourse. All observers have consequently tried to find some direct means of preservation by neutralizing the venereal poison inoculated during coitus.

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## I.—HISTORICAL SYNOPSIS.

White wine and vinegar were the first liquids which were prescribed. Nicolas Massa, a celebrated doctor of Venice, particularly recommends their use in the sixth chapter of his work *De Morbo Gallico* :

“*Quod si forte quis muliere infecta coïverit, laventur partes illæ post coïtum cum vino albo, vel cum aceto, quod magis placet, ut fiat confortatio membri et prohibitio corruptionis ad illam malam qualitatem et sic stet in suo robore membrum confirmatum.*” And later : “*Si vero quis cum infecta muliere coïre voluerit, quod fatuum est, lavetur vulva cum vino aut aceto et membrum virile cum aceto quoniam non sinit imprimere malam illam qualitatem et non moretur in coïtu—Et post lavetur membrum virile ut supra—Et contra, si mulier cum viro infecto coïverit, lavet viri membrum et vulvam et non morentur in coïtu.*”

Lime juice had also a certain amount of popularity. Fracastor, in his beautiful poem on syphilis, has celebrated its use in the following verses :—

“*Sed neque carminibus negluta silebere nostris  
Hesperidum decus et medarum gloria Citre  
Sylvarum . . . . .  
. . . . .  
Ergo ubi nitendum est cæcis te opponere morbi  
Seminibus, vi mira arbor cithereia præstat.*”

Gabriel Fallopius, who attached such importance to the prophylaxis of syphilis as to state that he would consider his work fruitless unless he had first taught men the means of protecting themselves against it, sang the praises of various lotions made from liquid preparations of mercury and guaiacum. These were applied to the glans, which was also

wrapped in a cloth covering, previously soaked in a decoction of aromatic and astringent herbs and dried. He swears that he tried these methods of preservation in several hundred cases, and that he had always been successful. "*Ego feri experimentum in centum et mille hominibus et Deum testor immortalem nullum eorum infectum.*" (*De Morbo Gallico Tractatus*, cap. lxxxix.)

Pierre Agathus (1564) had a good deal of praise for aromatic decoctions; Petronius, for lotions of urine and camphorated water. In 1690, Ettmuller, professor at Leipsic, advocated the use of oil of turpentine mixed with urine. Palamarius believed in the efficacy of a vinous decoction of guaiacum. De Mahon (1770) recommended washing the parts with a solution of alum. A year later, the English doctor Warren gave minute instructions on the subject, which consisted *ante coitum*, of rubbing on an astringent ointment; *post coitum*, in the use of lotions and injections made from an alkaline tartrate.

Guilbert de Préval (1772) prescribed a preservative composed of a mixture of distilled water, lime-water, alcohol, and corrosive sublimate. This brought on him all sorts of humiliations, and his name was struck off the list of regent doctors of the Faculty. "The learned Society, which at that time," says Langlebert, "only possessed in a very feeble degree that supremacy of Reason with which Voltaire had

just enlightened his century, made use of the occasion to censure all analogous methods, as opening the door to prostitution, and producing an upheaval that would do harm to the population, to common sense, and to the purity of morals."

In 1774, Peyrilhe proposed ammonia diluted with water. Hunter, Fordyce, Mederer, following Warren, recommended lotions and injections with a weak solution of caustic potash. This last liquid was already known in France under the name of *anti-venereal lotion*.

Hunter also prescribed, as useful in preventing venereal infection, lime-water and a solution of corrosive sublimate, in the proportion of 2 gr. to 8 oz. of water.

A little later, Dr. Malapert advocated the use, already indicated by Hunter, of a solution of bi-chloride of mercury.

In 1828, Coster, acting on the idea that chlorine had the property of destroying the syphilitic virus by taking away its hydrogen, made experiments on man and animals with chloride of sodium and chlorinated water. These experiments, it is said, were quite successful.

Chlorinated lotions and injections were prescribed to several individuals who frequently exposed themselves with infected women, and not one contracted venereal disease. Ricord, likewise, has

recommended the use of chlorinated lotions (water containing  $\frac{1}{5}$  of Labarraque's solution).

Acids and alkalies sufficiently diluted with water not to be too caustic, alcohol, aromatic wine, solutions of sulphate of zinc and acetate of lead, seemed to him to have been of some use; the efficacy of these substances, however, according to him, was confined to neutralizing the virus which had been deposited on tissues which were still healthy.

On the 7th November, 1812, Dr. Luna Calderon inaugurated a series of public experiments at the venereal hospital in Paris, to prove the preservative power of a method which he had invented; he scarified or incised the prepuce at some spot, which he covered with virulent pus. If he then applied his preservative, no chancre supervened; if, on the other hand, he did not apply it, the chancre appeared, and sometimes a bubo with it. Luna Calderon carried his secret with him to the grave.

Langlebert,<sup>1</sup> also, thought that he had found a prophylactic liquid.

|                                    |          |
|------------------------------------|----------|
| R Rectified Spirits at 40° Cartier | 40 grams |
| Soft Potassium Soap                | 40 grams |
| Dissolve and filter, then add      |          |
| Oil of Lemon (rectified)           | 20 grams |

He describes his experiments as follows: "Last

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<sup>1</sup> *Letters to Emile.*

Monday, 14th July, I took some pus from the surface of a phagedænic chancre with an indurated base, which I immediately inoculated into the left thigh of M. R—; then dipping my lancet in the same pus, I scarified the right thigh, so as to remove over a small area the epidermis and some of the dermis. When I had done this, in order to be quite sure of my experiment, I repeatedly dipped my lancet in the virulent pus, which I deposited quite warm, and, so to speak, quite living, layer by layer, on the wound to be treated. I waited then from five to six minutes before applying my preservative. The next day the inoculated pus on the left thigh had produced its usual effect; there was an inflamed papule, surmounted by a small vesicle at the point of inoculation; whilst the right thigh, which, I repeat, had been inoculated under the most favourable circumstances for the action of the virus, showed nothing apart from a small scab, which covered the wound I had made.”<sup>1</sup>

In Germany, about six years ago, Dr. Behrmann,<sup>2</sup> of Nuremburg, reasoning on the ground that mercury is a sovereign remedy against syphilis, proposed the use of friction with grey mercurial ointment as a preventive method.

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<sup>1</sup> Langlebert, *Letters to the Academy of Medicine*, 22 July, 1851.

<sup>2</sup> *Dermatologisches Centralblatt*, 1900, p. 172.



He advised that the genital organs should be well rubbed for several minutes with 3 to 5 grams (45 to 75 gr.) of this ointment. The first friction should be made as soon as possible after the suspicious contact. The second may be done on the following day.

Dr. Cohn,<sup>1</sup> of Berlin, proposed a modification of this method, which consisted of the application before coitus of an ointment composed of Ledermann's mercurial preparation, to which resorcin had been added. After intercourse, he advocated washing with a mercurial soap.

In France, Dr. Guiard,<sup>2</sup> of Paris, proposed another method, and advised the use of ablutions with solutions of sublimate, 1-4000 to 1-5000. He believes that, were prostitutes to employ this simple method, syphilis would spread much less than it does at present.

Following the German authors quoted above, Guiard's reasons for what he proposed were based on the well-known efficacy of mercury and its salts.

More recently, Dr. Bonnet,<sup>3</sup> of Lyons, in a thesis written under the direction of Professor Augagneur, advocated the use of calomel ointment during sexual intercourse. He does not state, however, that he

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<sup>1</sup> *Dermatologisches Centralblatt*, 1901, p. 237.

<sup>2</sup> *Annales de Dermatologie et de Syphiligraphie*.

<sup>3</sup> *Prophylaxis of Syphilis*, 1904.

considered it capable of preventing the generalization of syphilis once the virus has been deposited in the cutaneous lesion.

According to him, calomel ointment prevents the virus from coming in contact with the mucous surface or the skin, and at the same time neutralizes the action of the spirilla, owing to its anti-microbic properties.

This short synopsis indicates how numerous have been the efforts made to discover some preventive remedy against the disease. The preparations recommended in order to obtain the desired result have been equally numerous.

*A priori*, this multiplicity would seem to prove their inefficacy. This is, to a certain extent, true, for the actually-known qualities of some of the liquids employed cannot allow us to attribute to them a preventive value greater than that of pure water.

On the other hand, the solutions and ointment of mercury do, perhaps, possess the qualities claimed for them by their authors; but what proofs can they give of their efficacy? Oftener than not they have furnished none sounder than their own affirmation, which is certainly inadequate.

In some cases, a few medical men have experimented on man; they inoculated pus obtained from chancres, subsequently applying their preparations

to the spots on which they had previously smeared their virus, and they declare that oftener than not their preparations prevented the development of syphilis.

Unfortunately, a close study of these observations shows that in the fortunate cases the experimenters had merely to deal with virus from chancroids, and never with the true syphilitic virus.

#### CONCLUSIONS.

1. *Numerous chemical substances have been employed as a preventive measure against syphilis.*

2. *Most of the authors give no proof of their statements; and the remainder, starting from wrong principles, have naturally come to wrong conclusions.*

3. *It is only recent investigations on the subject which give us the hope of discovering a prophylactic remedy whose efficacy could be scientifically demonstrated.*

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#### II.—RECENT EXPERIMENTS ON PROPHYLAXIS.

1. **Experiments on Monkeys.**—When it was discovered that the anthropoid apes and the inferior catarrhini could be inoculated with syphilis, the study of the question of prophylaxis by means of

experiments followed as a natural consequence, and it was in this way that Metchnikoff and Roux studied the question.

As we have stated in a previous chapter, they ascertained that the syphilitic virus was so frail, that *heat* at 48° C. for half an hour *in vitro* was sufficient to render it harmless; this observation led them to think that prolonged heating of the inoculated spot might destroy the virus *in loco*.

"To elucidate this question, we inoculated," they state, "the penis of a papion (*C. sphinx*) with virus from the indurated chancres of two syphilitic individuals. An hour later we immersed the penis of the animal in warm water gradually heated to 48° C.

"The organ remained in the water, which was kept at this temperature, for forty minutes. This treatment did not hinder the development of two small oval indurations of syphilitic nature on the penis, and though the lesion proved to be of a very mild nature, and healed in a short time, nevertheless the experiment demonstrated the inefficacy of heat in the conditions we had chosen.

"The application of a *solution of sublimate* did not give any better result.

"We inoculated a macacus (*M. cynomolgus*) in the region of the eyebrows with virus from a human syphilitic chancre, and subsequently washed the

inoculated area with a 1 per cent solution for four minutes. After an incubation period of twenty-three days, the macacus presented on both eyebrows small suspicious lesions, slightly developed, which healed in a few days. The primary lesion, as in the preceding experiment, proved to be only slight, but our treatment did not succeed in completely preventing it.

“With the object of destroying the virus after inoculation by means of antiseptics, we again carried out several experiments with mercurial ointments.

“A chimpanzee was inoculated on both eyebrows with virus derived from two individuals suffering from indurated chancres; three-quarters of an hour after, the inoculated areas were rubbed for ten minutes with the double mercurial ointment (mercury, 100 gr.; benzoated lard, 100 gr.). This treatment caused some irritation on the left side, followed by local inflammation of the eyebrow, and some days later this area was covered by a dry slough, which finally separated.

“However, there was no sign of any syphilitic lesion. This result cannot be ascribed to the innocuousness of the inoculated virus, for a second chimpanzee, which was inoculated the same day with the same virus over the same regions, presented, after an incubation period of twenty-eight days, well-marked syphilitic chancres on both eyebrows.

"It was not the violent irritation caused by rubbing which prevented the appearance of the chancre, inasmuch as the right eyebrow, on which friction had not caused any inflammation or sloughing, was equally free. The short time which elapsed between the inoculation of the virus and the formation of the slough on the left eyebrow, as well as the appearance of the lesion and the absence of enlarged glands, would have sufficed to confirm the fact that we were not dealing with a syphilitic affection. To make assurance doubly sure, forty days after the first inoculation we carried out a second inoculation on the same chimpanzee with human virus. We inoculated both eyebrows, the penis, and the lower lip with virus from two syphilitics: thirty days after this inoculation (that is seventy-nine days after the first), a most typical chancre developed on the left eyebrow, followed six days after by the enlargement of the post-auricular lymphatic glands. Two typical chancres appeared on the penis nine days later, followed by enlargement of the inguinal glands.

"About a month after the onset of the primary lesion, a characteristic mucous patch appeared on the lower lip.

"This experiment conclusively proves that the virus of the first inoculation had been destroyed by the mercury without giving the slightest immunity to a subsequent inoculation of syphilis.

“Mercurial ointment has, then, the property of arresting syphilitic manifestations when employed an hour after the inoculation of the virus, but it has the disadvantage of being too irritating. This led us to search for some other preparation of mercury which might give us a better result. We had recourse to calomel ointment, the local use of which is so widespread in therapeutics.

“A chimpanzee was inoculated on both eyebrows with virus derived from the indurated chancres of two syphilitic individuals.

“After an hour and a quarter the inoculated regions were rubbed for five minutes with an ointment made up of 10 parts calomel and 20 parts lanolin. The animal died thirty-two days later from bronchopneumonia, without presenting any syphilitic lesion.

“A macaque (*M. cynomolgus*), treated in an exactly similar manner, lived 110 days from the onset of the experiment. Like the chimpanzee, it remained quite free from any lesion due to irritation, either of the ointment or of the inoculated virus.

“A cynocephalus (*Papion sphinx*) was inoculated on both eyebrows with virus from indurated chancres of the penis derived from two syphilitic patients.

“An hour after the inoculation the two eyebrows were rubbed with calomel ointment. On the next day these regions were found to be red, and traces of the scarifications were still visible. However, no

inflammation occurred, and the wounds healed in a short time. No syphilitic lesion appeared in the space of two months; whilst the control cynocephalus, which was inoculated with the same virus and left untreated, presented on the left eyebrow, after a lapse of forty days, a most typical chancre.

“Two months after the first inoculation the treated cynocephalus was re-inoculated on both eyebrows with virus from a human syphilitic chancre. Twenty-four days later this animal presented two red spots at the points of inoculation, at first barely characteristic, but which took later on the typical appearance of a primary lesion.

“This test inoculation confirms the fact that the calomel ointment hindered the action of the virus of the first inoculation.

“In another experiment, three macaques (*M. cynomolgus*) were inoculated on both eyebrows with virus derived from indurated chancres of the penis from two individuals suffering from syphilis.

“One of the macaques was reserved to control the experiment, whilst the two others received local treatment with calomel ointment an hour after the inoculation. The former presented typical chancres on both eyebrows after an incubation period of twenty-eight days, whilst the two that had been treated remained free from any lesion for the sixty-eight days during which the experiment lasted.



“Neither did the calomel ointment in these cases cause the least irritation.

“The results of the above experiments showed that the local treatment of the regions inoculated with syphilitic virus prevents the appearance of the disease; it therefore became a matter of great importance to find out how long the virus remains localized at the spot of inoculation. To solve this question, we inoculated the tip of the ear of a macaque (*M. cynomolgus*) with virus from an indurated chancre of the penis of a syphilitic patient. On the following day, twenty-four hours after the inoculation, we excised the inoculated area of the ear. The monkey did not develop any syphilitic lesions; when we made a second inoculation on the eyebrows sixty days later, the same animal presented typical syphilitic chancres on both sides. It follows, then, that the virus of the first inoculation did not go beyond the extremity of the ear, where it had been injected, and that the syphilitic virus had remained localized for at least twenty-four hours.

“A chimpanzee and a cynocephalus were both inoculated on the ear, in order to ascertain the time required for the virus to become generalized, but both died before the conclusion of the experiment.”

After this communication, Metchnikoff and Roux continued their observations, and further increased the number of experiments on the prophylaxis of syphilis of monkeys by mercurial ointments.

On the 8th May, 1906, Metchnikoff communicated the following to the *Academy of Medicine*:—

“A female chimpanzee was inoculated on the labia minora and clitoris, and a large papion received a large injection of the same virus on both sides of the penis. An hour after the inoculation the inoculated regions were rubbed with calomel ointment.

“Another chimpanzee and several macaques and cynocephalus apes were inoculated on the eyebrows, which were rubbed with calomel, white precipitate, and salicyl-arsenite of mercury ointments from one to eighteen hours after the inoculation.

“The results were always the same—the virus had no effect. Yet the virus used in these experiments was quite active, for it caused the typical primary lesion in the monkeys used to control the experiment, which were not submitted to the treatment. Several of the animals that had resisted the affection, owing to the use of these ointments, were subsequently re-inoculated with syphilitic virus, and presented later the typical primary lesion, thus proving that they did not possess any natural immunity as regards syphilis.”

## CONCLUSIONS.

1. *Mercury is even a greater specific against the local disease than against the general disease.*

2. *Liquids and solutions containing mercury are inefficacious.*

3. *Fatty mercurial preparations, employed from one to eighteen and a half hours after inoculation, have always prevented the appearance of the pox in the monkey.*

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2. **Experiments on Man.**—In the course of our medical studies we had our attention drawn to the famous communications of Roux and Metchnikoff on the receptivity of the simian species.

On reading the pages we have just quoted from the *Annales de l'Institut Pasteur*, we, in common with all who had read them, became highly interested in the subject.

Many naturally objected, and their objections carried some weight, that the monkey is not entirely comparable to man, and that it would be impossible to affirm that these experiments would give the same results in man. This suggested to us the idea to propose to MM. Metchnikoff and Roux to submit ourselves to the same inoculations and to the same preventive treatment, which had proved such a success when applied to the simian species.

After hesitating a good deal, the two great savants finally accepted this proposal. It was, however, decided that we should wait until a current experiment, the one last mentioned, was completed.

**Bodily State of M. Maisonneuve**, according to the examination carried out on the 23rd January, 1906, by Drs. Sabouraud and Salmon.

*Subjective Examination.*—M. M—— swears that he has no antecedent hereditary syphilis, nor has he ever had syphilis himself.

*Objective Examination.*—The buccal mucous membrane, the tongue, and the tonsils are normal.

There are no enlarged glands in the neck, mastoid, or epitrochlear regions.

The lymphatic glands in both axillæ are enlarged.

In the right inguinal region there is a small, slightly enlarged, and painful lymphatic gland, due to an eruption of herpes on the penis; there are two small herpetic vesicles on the mucous surface of the prepuce, as well as three or four confluent vesicles in the sulcus, both situated dorsally.

**Inoculation**, on the 1st February, 1906. M. M—— is cured of his herpes; there is no longer any enlargement of the glands in the right groin. M. Metchnikoff performs the inoculation, in presence of MM. Roux, Queyrat, Sabouraud, and Salmon.

“With a Vidal’s scarifier,” says Metchnikoff, “I made three parallel scarifications on the left side of the sulcus coronæ. The scarifier was smeared with virus from the chancre of M. D——.

"I immediately performed a similar inoculation on the right side of the sulcus coronæ with virus from M. O. L——."

*Patients.*—M. D—— is a patient from M. Humbert's wards. He is twenty years of age, and has an indurated chancre on the frenum of the penis, of a month's duration, suppurating balanitis, enlarged glands in both groins, and no roseola. He has had local treatment with nitrate of silver.

M. O. L—— is a patient from the wards of M. Queyrat. He is suffering from an indurated chancre of the penis of nine to ten days duration. Enlargement of the inguinal glands. No roseola; has had no treatment, general or local.

*Application of the Prophylactic Treatment.*—An hour after the inoculation, the penis of M. M—— was rubbed for five minutes with calomel ointment (calomel 10 gr., lanolin 30 gr.).

## Monkeys used to Control the Experiments.

### I. TO CONTROL THE VIRUS.

1. *Chimpanzee, No. 46.* This chimpanzee was inoculated on the left eyebrow with virus from M. D——, and on the right eyebrow with virus from M. O. L—— some minutes after M. M——.

10th February.—The chimpanzee dies from pneumonia before the disease could have had time to manifest itself.

2. *Macacus cynomolgus, No. 61.*—On 1st February, 1906, at the same time as M. M——, this macaque was

inoculated on the left eyebrow with virus from M. D—, and on the right eyebrow with virus from M. O. L—.

18th February.—There has appeared on the right eyebrow a syphilitic lesion (primary lesion).

28th February.—The primary lesion is healing.

12th March.—The primary lesion is completely healed.

3. *Macacus cynomolgus*, No. 62.—On 1st February, 1906, inoculations as in No. 61.

On the 18th there appeared on the right eyebrow a typical syphilitic lesion.

28th February.—The primary lesion is well developed and characteristic.

12th March.—The primary lesion is still well marked.

3rd May.—The primary lesion is still visible.

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## II. TO CONTROL THE PREVENTIVE ACTION OF THE OINTMENT.

1. *Macacus Cynomolgus*, No. 63.—1st February, 1906.—Inoculations as in macaques, Nos. 61 and 62.

An hour after the inoculations, the two eyebrows were rubbed for five minutes with calomel ointment (the same as that used for M. M—).

17th February.—Nil.

28th February.—On the right eyebrow there are a few lesions, which the animal inflicted on itself by knocking itself against the bars of the cage.

14th March.—The only things to be seen are the cicatrices of these small lesions, which could never have been confused with the primary lesion.

2. *Macacus cynomolgus*, No. 64.—1st February, 1906.—Inoculations as in macaques, Nos. 61, 62 and 63.

2nd February.—Twenty hours after the inoculations the two eyebrows were rubbed with calomel ointment for five minutes. (The ointment was the same as that employed for M. M—— and for the macaque, No. 63.)

17th and 28th of the same month.—Nil.

12th March.—Small lesions on the right eyebrow of a doubtful character. (It is too early to venture on a diagnosis.)

14th March.—The lesions on the right eyebrow have markedly increased. They are of a reddish colour, and have the same aspect as that of a primary lesion.

17th March.—The macaque has been found dead. The appearance of the lesions on the right eyebrow leaves no doubt as to their specificity.

### Result of the Experiment performed on M. M——.

3rd February.—No inflammation of the sulcus coronæ. Examination with a magnifying-glass still shows a trace of the scarifications—very small wounds invisible to the naked eye.

These wounds do not show the least evidence of inflammation. The remains of the calomel ointment still adherent were removed by scraping. No powder or dressing applied.

5th February.—The small scarifications are healed.

During these four days there was no itching or irritation due either to the application of the ointment or to the wounds of inoculation.

7th February.—The points of inoculation are normal.

On the mucous surface of the prepuce towards the dorsal aspect of the penis there are two small suppurating vesicles, smaller than herpes vesicles.

*9th February.*—These vesicles have disappeared.

*12th February.*—Appearance of prepuce and glans normal.

*15th February.*—Appearance of prepuce and glans normal.

*19th February.*—On the mucous surface of the prepuce there are four small suppurating vesicles.

*21st February.*—The healed vesicles have left a red mark.

*23rd–28th February.*—All is normal. Nothing to be seen at the points of inoculation, nor anywhere else, save a slight reddening at the region of the vesicles of the 19th.

*2nd March–12th April.*—M. M—— is seen on the 5th, 7th, 9th, 11th, 13th, 15th, 19th, 23rd, 27th, 30th March, and then again on the 4th and 8th April; everything is quite normal.

*12th April.*—Seventieth day of experiment, no cutaneous syphilitic lesion; examination of the inguinal region shows no enlargement of the lymphatic glands.

M. M—— is suffering at present from six small ulcerated lesions on the prepuce—lesions which are not situated at the points of inoculation, and are plainly due to an eruption of herpes.

*17th April.*—Seventy-fifth day after the inoculation; the lesions have healed, leaving merely a slight reddening.

On the 6th May, 1906, the ninety-fourth day of the experiment, we submitted ourselves to the examination of MM. Sabouraud and Salmon.



**Examination by MM. Sabouraud and Salmon.**—On the 6th May, 1906, a thorough examination of M. Maisonneuve reveals no trace of recent syphilis.

The skin of the body shows a few active acne spots, and some scars of former acne.

The lymphatic glands of all regions are free from inflammation and are normal.

The buccal mucous membrane and the anal mucous membrane do not present any lesions

On the dorsal aspect of the mucous surface of the prepuce there is a small cluster of typical herpes lesions, three vesicles on one part, and two a little further on, exactly similar to those which the patient suffers from periodically, and which we had the opportunity of noticing once, before he began his experiment.

(Signed) SABOURAUD, SALMON.

*6th May, 1906.*

On the 8th May, 1906, we went to see Dr. Queyrat, who in his turn examined us.

**Examination by M. Queyrat.**—At the request of Prof. Metchnikoff, I was present on the 1st February, 1906, at the inoculation of M. Maisonneuve with syphilitic virus; he was at the time free from syphilis. The points of inoculation were treated one hour after with calomel ointment (1 part calomel to 3 of lanolin).

M. Maisonneuve came to-day, 8th May, to submit himself to my examination; he has not any lesions, and though I examined him with the greatest care, I did not find anywhere the least trace of any syphilitic infection.

There is nothing on the trunk, apart from some acne ; no syphilides to be seen anywhere ; the mucous membranes of the mouth, tongue, and throat, as well as that of the anus, are free from any lesions, and are quite normal.

The inguinal, cervical, and epitrochlear glands are normal. The hairs are strongly implanted, and cannot be pulled off, even by using considerable force.

There is nothing to be seen in the palms of the hands.

The inoculations performed in the region of the sulcus coronæ have not left the least trace, nor any induration.

I find on the mucous surface of the prepuce, in the median line and also to the left, two small erosions which are in process of healing ; these are plainly erosions due to herpes, to which M. Maisonneuve is subject, and were the results of small vesicles which were present three or four days previously. I repeat that I consider M. Maisonneuve to be free at present from syphilis.

(Signed) QUEYRAT.

*Paris, 8th May, 1906.*

#### REPORT TO THE ACADEMY OF MEDICINE.

On the 8th May, 1906, M. Metchnikoff, speaking for Dr. Roux and for himself, reported to the Academy of Medicine, "Some New Facts Concerning Experimental Syphilis."

After he had recalled to the Assembly the results of experiments on animals, M. Metchnikoff continued as follows :—

"Having obtained on twelve monkeys the most

satisfactory results, we saw no reason why we should not try the experiment on man. Among several persons who had offered themselves for this purpose was a young medical student of the Faculty of Paris. He had completed his medical studies, and was perfectly aware of the nature of the question, and, therefore, could act with full knowledge of what he was doing.

"This young student never had syphilis, hereditary or acquired. Persuaded as we were that the method which had proved efficacious for monkeys would also prove so for man, we did not think that he ran any serious risk of contracting the disease. We, therefore, on the 1st February of the current year, in presence of Drs. Queyrat, Sabouraud, and Salmon, carried out the following experiment: On the left side of the sulcus coronæ we made three parallel scarifications with a Vidal's scarifier smeared with syphilitic virus. This latter had just been derived from an indurated chancre of a patient in the wards of M. Humbert. The chancre dated a month back, and was accompanied by enlarged glands of both groins. Immediately after, and by the same method, we inoculated the right sulcus with syphilitic virus derived from an indurated chancre of nine to ten days' duration, of one of Dr. Queyrat's patients. He had some enlargement of the inguinal glands, and had not undergone any treatment.

"The virus from the same two patients was inoculated on the same day into a chimpanzee (which died two days later from pneumonia, without having given any positive result), and also into the eyebrows of four Java macaques.

"An hour after the inoculation of the virus, the

lesions of the student and of one macaque were rubbed during five minutes with a recently prepared ointment containing 10 grs. of calomel and 30 of lanolin. Twenty hours after the inoculation, the eyebrows of a second macaque were thoroughly rubbed with the same ointment. Two other monkeys were left untreated, so as to check the results of the experiment.

“On the third day of the experiment the inoculated region in the patient presented no evidence of inflammation; traces of the scarification made could be still distinguished on both sides of the penis by means of a magnifying-glass. They disappeared a few days later.

“Subsequently, our patient presented on the free border of the prepuce, far from the inoculated areas, small vesicles filled with pus. These vesicles, which looked like herpes, disappeared in two days; they had absolutely no connection with syphilis. The lymphatic glands in the groins did not show any hypertrophy. The young man is liable to these eruptions, and he had similar vesicles some time before the beginning of the experiment.

“We must conclude from this, that in spite of an inoculation with syphilitic virus in much greater quantity than is possible under natural conditions, our young patient remained completely free from syphilis.

“This immunity cannot possibly be attributed to innocuousness of the virus employed, for seventeen days after the commencement of the experiment the two macaques that had not been treated with the ointment, presented along the right eyebrow lesions exactly similar to those of the numerous other syphilitic

monkeys in our previous experiments. The primary lesion in one of the monkeys healed in three weeks ; it was, however, extremely well developed in the other, and is still present more than two and a half months after its appearance.

“ Of the two monkeys rubbed with calomel ointment, the one that had been rubbed twenty hours after the inoculation of the virus presented a primary lesion of the right eyebrow after an incubation period of thirty-nine days. The other, treated at the same time as the young student, showed no signs of any syphilitic lesion.

“ This experiment, the details of which will be published in the thesis of our patient, furnishes us with the proof that calomel ointment, applied one hour after an inoculation of syphilitic virus, is capable of preventing the onset of the disease quite as much in man as in the monkey.

“ It also proves that the ointment loses its preventive influence within twenty hours after the inoculation. From the collection of these observations in man and monkey we are justified in coming to the conclusion, that an ointment containing calomel is useful as a prophylactic measure against syphilis. Further experiments, some of which are now in progress, will enable us to give more precise details on the preventive use of mercurial ointments.”

M. HALLOPEAU.—“ The report communicated by M. Metchnikoff cannot fail to prove of widespread interest ; Neisser, however, at the Congress of Lisbon, declared that he was unsuccessful, although he operated in a manner similar to that described. If the facts brought forward by M. Metchnikoff prove to be correct,

the old quarrel between those who advocate the supervision of prostitution and those who desire its abolition will come to an end, for every one who has his little pot of calomel ointment would have no need to occupy himself with the health of his partner.

“Moreover, if syphilis disappeared, tabes and general paralysis would likewise disappear.

“I shall ask M. Metchnikoff whether he has ever noticed any local irritation due to the use of calomel ointment ?”

M. METCHNIKOFF.—“It seems almost a confirmation of the success of our experiments that M. Neisser, in repeating them, did not obtain any success, for we know that for a long time Neisser failed to produce syphilis in monkeys, when we, as well as other experimenters, were easily successful.

“I must admit that the experiment carried out on the young student is incomplete, because a counter-experiment was not done at the same time. This would consist in inoculating syphilitic virus into a man without carrying out local treatment with calomel ointment. But we cannot act with man as with animals; and therefore the experiment necessarily remained incomplete. Nevertheless, I believe that it is of the greatest value, especially if it be taken in conjunction with the following incident.

“I was scratched by a syphilitic monkey, and immediately rubbed the part with calomel ointment; not the slightest sign of syphilis supervened. In my experiments I have used calomel as well as enesol

ointment<sup>1</sup> with success, and without causing the least inconvenience. I have never seen any irritation result, except from the use of grey ointment."

After the issue of this report the experiment was considered to be at an end. Very soon after, however, some of the organs of the Press spread the rumour that I had contracted syphilis. In consequence of this statement, and in the absence of M. Metchnikoff, M. Roux was eager to prove by a fresh examination that these rumours were unfounded, and after having examined me, sent to the editor of the *Temps* the following denial:—

PARIS, 31st May, 7.0 p.m.

SIR,

You have interviewed me, to ascertain whether it is true, as certain journals have stated this morning, that the medical student who had submitted himself to the experimental inoculation of syphilis, and had been treated subsequently with a local application of calomel ointment, had contracted the disease.

You may deny this rumour absolutely. I have just seen the young doctor, and he is in perfect health.

Moreover, the time which has elapsed since the inoculation (120 days) is sufficient to consider the experiment as being at an end.

(Signed) DR. ROUX.

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<sup>1</sup> Enesol is a salt of mercury (salicylarsenate of mercury) containing 38.46 per cent of mercury; it is an amorphous powder, soluble in twenty-five times its weight in water.

## OBJECTIONS OF PROFESSOR NEISSER.

In the discussion which followed the communication made by M. Metchnikoff at the Academy of Medicine, M. Hallopeau alluded to the report which had been made at the Congress of Lisbon by Prof. Neisser.

M. Metchnikoff, who was unaware at the time of the exact expressions of which Prof. Neisser had made use, could only reply by bringing forward new arguments.

Since then the report of the Professor of Breslau has been published in the May number (1906) of the *Société Française de Prophylaxie Sanitaire et Morale*. The following is the passage in which the German professor formulates his opinion on the experiments of Metchnikoff :—

“ I must confess that the most important problem has not yet been elucidated, viz., as to how far we can rely on the fact of local success being followed by a complete and definite cure. This objection, which can be raised against all those apparently successful cases of excision, can also be brought forward against the experiments of M. Metchnikoff. He states in his communication, ‘ We have found that the ointments prepared from salts of mercury destroy the syphilitic virus. We have applied this method



to macaques, papions, and chimpanzees, and have always obtained positive results.'

"I, on my part, carried out the same experiments, but unfortunately the results obtained have not always been positive. Even the use of mercurial ointment an hour after the inoculation did not prevent the development of the chancre. This shows how difficult it is to lay down a general law, when the numerous causes of error, and the difference of method in carrying out the experiments, are taken into account. Perhaps M. Metchnikoff's inoculations were more superficial than mine. This would then be a natural explanation of the different results obtained with the use of mercurial ointments."

M. METCHNIKOFF'S REPLY (communicated orally).

To *the first objection*, which consists in making a distinction between local and general cure, M. Metchnikoff replies that he re-inoculated with syphilis most of the monkeys treated by calomel ointment after the lapse of a definite period. On this second occasion no preventive treatment was carried out. In all these cases re-inoculation proved positive, showing that calomel ointment had really protected the monkeys treated by this method.

To *the second objection* raised by Prof. Neisser, viz., that he did not succeed in preventing the onset of syphilis by using mercurial ointments, M. Metchnikoff

brings forward the results of his experiments, which were all successful, except when friction was carried out twenty hours after the inoculation.

The most probable explanation of the difference between Neisser's results and those obtained by himself is furnished by Neisser himself, who submits the hypothesis that "perhaps M. Metchnikoff's inoculations were much more superficial than mine."

Yet, in spite of these deeper inoculations, he records some successful cases, thus affording further evidence of the efficacy of the ointment.

Ordinarily the lesions of those who contract the disease are still more superficial than those made by M. Metchnikoff. *We are, therefore, justified in concluding that ordinarily the use of calomel ointment, within a definitely short period of the inoculation of the virus, constitutes an efficient means of preventing the onset of syphilis.*

We can, moreover, give definite details on the depth of the cutaneous wound in our case, made by the scarifier of the experimenter, M. Metchnikoff. The multiple lesions, viz., the six incisions made by the scarifier, were visible for four days; on the fifth day they were not visible, and had cicatrized. These, then, were superficial lesions, which were, however, from our experience of the virus, quite sufficient for syphilitic inoculation.

## CHAPTER V.

### PRACTICAL APPLICATION.

PROFESSIONAL SYPHILITIC CONTAGION (MEDICAL MEN, DENTAL SURGEONS, MIDWIVES, WET-NURSES, NURSES, ETC.)—VENEREAL SYPHILITIC CONTAGION.

THE experiments of MM. Metchnikoff and Roux show that calomel ointment has a distinct action on the syphilitic virus.

When used in the monkey from one to eighteen and a half hours after inoculation, it prevents the appearance of the primary lesion, as well as what was known in the time of Diday and Ricord as constitutional syphilis.

This fact is demonstrated by a series of twelve experiments, in which MM. Metchnikoff and Roux had not to record a single unsuccessful case.

It is quite easy to understand that it has been impossible to carry out as many experiments on man. But there is one case to record, which is wholly in favour of the method; an hour after the inoculation the parts were rubbed, and syphilis was not contracted.

Additional experiments will naturally prove of great interest, but the fact that ours has succeeded proves that in man, as in monkey, the spirillum requires a certain time before it invades the organism.

The similarity in the time of incubation in man and in monkey enabled us to forecast this result.

Authorities on syphilis such as M. Hallopeau have enquired whether calomel ointment would not have a pernicious influence on the tissues; M. Metchnikoff has, however, been able to state that the ointment in his hands had never produced the least irritation in man or in monkey.

It seems then fairly established, that we possess a therapeutical agent of undoubted value as a preventive against syphilis, and that this drug, used according to certain rules, does not give rise to the least inconvenience. The value of the discovery made by MM. Metchnikoff and Roux can easily be conceived when we think of the incalculable number of people to whom it will prove useful.

Foremost are those whose profession exposes them daily to the risk of contracting syphilis. These are medical men, accoucheurs, dentists, midwives, and nurses, who, though they constitute but a small minority, are the first to attract our attention, owing to the special manner in which they are liable to be infected.

A medical man or an accoucheur does a rectal or

vaginal examination on a patient who is suffering from an unrecognized chancre or from mucous patches, which are common in those regions ; he has some slight unnoticed scratch or abrasion of his exploring finger with which the virus comes in contact ; as a result he falls a victim to syphilis.

A nurse may have to dress a more or less bleeding wound, with which her dermis, laid bare by some slight abrasion, comes in contact ; the dressing done, it is noticed that the wounded man has specific symptoms ; as it is too late to do anything, the unfortunate nurse has to spend a long and anxious time before acquiring any certainty of being free from the disease.

Dentists are also liable to contract the disease in the exercise of their profession. It is indeed known that mercurial stomatitis appears oftener and with greater intensity among individuals who take little care of their mouth ; as a rule, these people are recommended, before commencing a course of mercurial treatment, to have their teeth attended to, to have any carious teeth extracted or filled, to have any tartar scraped away, and, in a word, to have all causes of secondary infection removed.

In carrying out any of the above operations, a dental surgeon may easily sustain a slight wound or abrasion through a broken tooth, through which the virus can penetrate into the organism.

Henceforth, whenever the examination of a syphilitic patient necessitates direct contact, from which a wound results, nothing will be easier than to rub in calomel ointment at the spot where the virus may have entered.

Salmon has related to the *Société de Prophylaxie Sanitaire et Morale* the case of a midwife, who noticing that she had a scratch on the hands a short while after she had examined an undoubtedly syphilitic woman, made use of calomel ointment, and never suffered from any specific lesion. Naturally, this case has not the value of a laboratory experiment, but it is none the less interesting, and shows the advantage to be derived from this prophylactic method. Salmon<sup>1</sup> and Macé have laid stress on the danger of infection to wet-nurses from the handling of children who suffer from syphilitic pemphigus bullæ.

In addition to professional contagion, there is, of course, the much more common method of venereal contagion.

On account of the extreme importance of this means of propagation of syphilis, we shall describe in a few words the most logical method of using the ointment.

Fatty substances, such as vaselin, are frequently used in sexual intercourse, to lubricate the copulating

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<sup>1</sup>Obstetrical Society of Paris, 1905.

organs. Therefore, one of the best ways of employing calomel ointment would be to use it instead of these fatty bodies.

In this way the ointment is placed exactly on that part with which the virus is most likely to come in contact ; moreover, the movements of coitus cause the necessary friction which is required for the penetration of the mercury into the tissues ; lastly, there is the further advantage that both the man and the woman are protected.

This would be the ideal way of using it, particularly for the woman, in whom friction of the vaginal walls is barely possible except at the vulva.

It is, moreover, noticeable that chancres diminish in frequency the further the distance from the vulvar orifice ; there are chances then that syphilis will be prevented, by rubbing the labia and the most external portion of the vagina.

It would be best to carry out this friction within an hour after the doubtful intercourse ; there is, however, a whole class of prostitutes who could not act in this manner. In these cases the application of the ointment at intervals of eighteen hours would seem to be sufficient, from what experiments on monkeys have taught us.

As far as man is concerned, if he should not use the ointment during coitus, the sexual act once accomplished, he will be conscious of the danger he

runs, and will take care to protect himself from a possible infection.

In this case, he should rub the genital organs—the penis, and chiefly the prepuce and the glans—for about five minutes ; this should be done as soon as possible after the suspicious intercourse.

We need scarcely state again that this friction was made on man only one hour after inoculation ; we are, however, justified in thinking, from experiments on monkeys, that this would still be efficacious several hours after the deposition of the virus.

Experiments, which are at present being carried out, will shortly enable us to give more precise details on the subject ; we have, however, already acquired the knowledge that calomel ointment is a substance capable of arresting the onset of syphilis for a period sufficiently long after inoculation to render it very useful in practice.

It is an undoubted fact that the use of calomel ointment will prevent the onset of syphilis.



## CHAPTER VI.

## GENERAL CONCLUSIONS.

1. All syphilitic lesions are contagious and inoculable : primary, secondary, and tertiary lesions alike.

However, it is only in exceptional cases that it has been possible to inoculate gummata successfully into monkeys.

2. To contract syphilis, an individual must present some loss of continuity in his integuments.

It has been possible, experimentally, to ascertain the exact depth of the loss of continuity ; it must be dermo-epidermal.

3. It has been possible, thanks to the discovery of the pathogenic agent of the disease, the spirillum of Schaudinn and Hoffmann, to study and define the distribution of the virus in the different lesions of syphilis.

4. It is possible to act on the virus of syphilis deposited, as we have seen, in the superficial layer of the skin, and abort the disease as long as the virus has not invaded the organism.

Different experiments, especially those of MM. Metchnikoff and Roux, and Neisser, prove that the

time during which the disease remains local, and is capable of being influenced by prophylactic measures, is relatively short. It is much too late to prevent the infection of the organism when the chancre has appeared.

5. We have seen that it is possible to influence the virus (for it remains during a certain period localized and very superficial) by the use of physical or chemical agents. Of all these agents the one most likely, theoretically, to give the best results is mercury.

6. A historical survey shows us, that as soon as it was discovered that the disease was contagious (that is from the beginning of the sixteenth century), a large number of substances of doubtful efficacy have been recommended to prevent infection by the virus of syphilis.

7. The discovery of MM. Metchnikoff and Roux has enabled us to make a scientific study, by means of inoculation into animals, of the value of certain means of prophylaxis.

These scientists have discovered that mercury has a very marked preventive influence in destroying the virus at the point of inoculation from one to eighteen and a half hours after its deposition.

Mercurial ointment proved very active, but was irritating to the tissues ; on the other hand, calomel ointment was quite as efficacious and did not cause any irritation of the skin.

These experiments were carried out on twelve monkeys, and all proved successful.

8. In presence of these results, MM. Metchnikoff and Roux did not confine themselves to the simian species, but thought they were justified in carrying out an experiment on man.

In a man quite free from any syphilitic taint, hereditary or acquired, they inoculated by superficial scarification virus derived from two syphilitic chancres. This virus was active, and gave the disease to the animals employed to check the experiment, whilst the man, who was rubbed at the points of inoculation with calomel ointment an hour after, did not contract the disease.

9. We are justified in concluding from the results of these experiments, that the use of ointments containing mercury or salts of mercury (which are absorbed by the skin) protects from syphilitic infection, when they are used on the parts exposed to the contagion, e.g. the sexual organs after sexual intercourse.

This method of protection should also prove of great use to medical men, midwives, dentists, and nurses, who run the danger of contracting professional syphilis.

## APPENDIX I.

*Containing a résumé of the researches on the prophylactic use of calomel ointment carried out by MM. METCHNIKOFF and ROUX since the publication of this Thesis.*

MM. METCHNIKOFF and ROUX laid the result of our experiment before the Academy of Medicine on the 8th May, 1906. They have since actively prosecuted their researches on the prophylaxis of syphilis. Their aim has been to discover a vaccine against syphilis by attenuating the virus; they have, at the same time, tried to lay down certain definite rules of great practical importance on the use of calomel ointment.

These results will be found in their fifth report on "Experimental Studies of Syphilis," contained in the *Annales de l'Institut Pasteur* (October, 1906).

In this report will also be found a reply to the attacks and criticisms made in Germany by Prof. Neisser, of Breslau, as well as in France by Prof. Gaucher, and several others. We cannot, therefore, do better than reproduce *in extenso* the whole of that part of the report dealing with the subject in question.

"Although the fact has been established that the virus of syphilis can be attenuated, a good deal still remains to be done before an anti-syphilitic vaccine can prove of any practical use. We have tried, meanwhile, to discover some practical and harmless prophylactic measure.

"In two communications published by Dr. Roux and myself within the last year, a full account is given of the experiments we carried out on the prophylactic use of mercurial ointments. These show that mercurial ointments have the power, after the inoculation of the virus, of arresting the onset of syphilis, without, however, conferring the least immunity against the disease.

"After our report to the Academy of Medicine, M. Hallopeau brought forward as an objection to our experiments the results obtained by Prof. Neisser, who had failed to prevent the onset of syphilis in inoculated monkeys by means of calomel ointment. According to the report read by the famous German Professor at Berne, in September, 1905, he had made use of an ointment containing only 10 per cent instead of 25 to 33 per cent of calomel. The results, therefore, obtained by Prof. Neisser cannot be compared with ours, which renders it, perhaps, unnecessary to state that his inoculations were also deeper.

"In our inoculations we introduce the syphilitic virus not merely on the surface of the dermis, but intradermally, according to the method practised by Finger and Landsteiner. Our inoculations were in all cases deeper, more thorough, and more numerous, than that to which a man is liable when he contracts the disease in the ordinary way. We feel confident in stating that deeper inoculations are useless.

"The results of further experiments which we have lately carried out only help to confirm those previously made.

"To prove whether ointments containing less calomel were quite as efficacious as those we had formerly used, we inoculated five monkeys (*Cynocephalus Sphinx*) on the eyebrows with virus from a human syphilitic chancre. An hour after the experiment, two of their number

were rubbed with an ointment containing 1 part of calomel to 10 of lanolin, and two others with an ointment containing  $\frac{1}{5}$  part of calomel. The fifth monkey was kept untreated to check the result of the experiment.

“Of the four treated monkeys, one died before the end of the experiment, whilst the remaining three developed, after the usual incubation period, typical syphilitic chancres, two of them especially presenting very well-marked lesions.

“This experiment proves that the ointment, to be efficacious, must contain at least 25 per cent of calomel. We think that it is preferable to use an ointment containing 33 per cent of calomel, as we did in our previous experiments. The results of these experiments prove that the useful action of the ointment is due to the calomel, and not to the lanolin; as the ointments which contain a larger proportion of this latter substance have no preventive action. We should never have thought of insisting on this fact had it not been stated by some that the action of the ointment is due to the lanolin and not to the calomel.

“In another series of experiments, three Java macaques were inoculated on the eyebrows with virus from indurated chancres obtained from two syphilitics. Two of these animals were treated an hour after inoculation with an ointment containing 33 per cent of calomel, which was merely applied to the inoculated areas. The third monkey, which remained untreated, developed a well-marked primary lesion after an incubation period of twenty-five days, whilst the other two did not present the slightest lesion after an observation period extending over several months.

“These experiments of the preventive action of calomel ointment on monkeys are sufficiently numerous and satisfactory to serve as the basis of a prophylaxis of syphilis.

"On the repeated entreaties of M. Maisonneuve, a medical student in his final year, we extended them to man. We decided to inoculate him with syphilitic virus, followed by the use of an ointment containing 25 per cent of calomel. The result of this experiment was laid before the Academy of Medicine by Dr. Roux and myself, and is related with greater details in M. Maisonneuve's thesis. We specially note this experiment for the purpose of stating that it confirms the results already obtained in monkeys, for M. Maisonneuve was protected against the virus obtained from two syphilitic chancres, and inoculated with a scarifier on the penis in six different places.

"The virus in this experiment was undoubtedly introduced in a larger quantity, and in a more thorough manner, than is possible in the ordinary mode of infection.

"The critics of M. Maisonneuve's thesis questioned the value of this experiment, on the ground that it was solitary. They seemed to have taken no notice of the fact that it was the culminating point of a whole series of experiments on animals, which by themselves were quite sufficient to justify the prophylactic use of mercurial ointments. Prof. Gaucher, during the discussion on the thesis, quoted a case from his practice, where it would appear that the use of calomel ointment did not prevent the onset of syphilis. He, however, gave no details of the case, about which we have been unable to obtain any further information. We cannot, therefore, discuss it. On the other hand, we have found in the literature on the subject another case, the details of which are fully quoted by Dr. Crépet, in which the use of calomel ointment exercised its preventive action.

"The case in question was that of a man who, being

suspicious of the health of a woman with whom he had just had relations, immediately consulted a medical man. The latter diagnosed a well-marked secondary syphilitic infection in the woman, who was at the time suffering from mucous patches of the vulva and mouth.

"Dr. Crépet immediately ordered his friend, one hour and a half after the possibility of infection, to rub his genital organs as well as his lips for ten minutes with an ointment containing 1 part in 30 of yellow precipitate, and prescribed some *Van Swieten's lotion* to be used as a gargle and mouth wash.

"Some small erosions in his mouth were cauterized with silver nitrate. He was also advised to use Neapolitan ointment on the prepuce and glans for the following six weeks.

"In addition to the above, he was prescribed mercury internally in the form of the proto-iodide.

"The patient was kept under observation for three months, during which time 'he did not manifest the slightest syphilitic lesion, cutaneous, mucous, or glandular.' This case dates from the month of May, 1906. We believe that if Dr. Crépet had known of the experiment of Dr. Maisonneuve, which was only published in May, he would have simplified the preventive treatment, which he himself had found somewhat overdone.

"Though the ointment he prescribed contained much less mercury than ours, its use was extended over a more prolonged period.

"A second case of the preventive action of mercurial ointment, which we owe to Dr. Picquet, of Sens, has recently come to our notice. During the month of June last, a young man, an intimate friend of his, confided his anxiety to him. He had spent the night with a woman, and on waking up in the morning noticed an erosion on his penis. Having mentioned this to the



woman, she informed him that she also had 'some sores on the genitals, as well as a sore-throat.' She did not know the nature of her affection.

"On that same morning, at 8.30, Dr. Picquet diagnosed in his young friend the presence of a small erosion situated at the junction of the sulcus glandis, which had the appearance of a small ruptured herpes vesicle.

"On the same day, before mid-day, the young man had his companion of the previous night examined by Dr. Picquet, who detected the presence of typical mucous patches of the vulva and mouth, as well as multiple enlargement of the glands, symptoms of a well-marked and highly contagious syphilis.

"At 4 p.m., on the advice of Dr. Picquet, the patient rubbed his penis with calomel ointment (25 per cent), which he left on for forty-eight hours, and as a result remained absolutely free from any syphilitic lesion.

"Dr. Picquet, who is an old and intimate friend of his, declares that he has never suffered from acquired or hereditary syphilis.

"This case might, according to Dr. Picquet, almost be compared to a laboratory experiment. It is highly probable that without the application of calomel ointment the lesion of the penis (eruption of herpes in the present case) would have served as the door of entry to the syphilitic virus.

"Apart from scientific considerations, it has been stated that the preventive use of mercurial ointments was immoral, because it would tend to increase the number of extra-conjugal relations. But as all moral prophylactic measures have failed to arrest the spread of syphilis and the consequent infection of the innocent, what is immoral is to check the means of fighting the evil. The medical practitioner has no hesitation in

treating a syphilitic who has contracted the disease extra-conjugally, nor does he allow him to suffer from tertiary lesions so as to act as a kind of scare-crow, and serve the purpose of a moral lesson to others. The hygienist has equally to do his utmost to prevent the spread of the disease by all the means which science places at his disposal.

“We can conclude by stating that the experimental study of syphilis has shown the possibility of attenuating the virus by passage through the inferior apes, which gives us the hope that we may yet succeed in discovering a vaccine against the disease.

“It has, meanwhile, been conclusively proved that mercurial ointments have a preventive action against syphilis.”

*Additional Note.*—“Since the above was written, two articles on the preventive use of calomel ointment have been brought to our notice.

“In one of them, M. Lévy Bing (*Ann. des Malad. Ven.*, Sept., 1906, p. 119), relates the case which M. Gaucher alluded to when M. Maisonneuve’s thesis was under discussion.

“In the second article, Prof. Gaucher (*Ibid.*, Oct., 1906, p. 320) relates the case of a medical man who contracted the disease in spite of the preventive use of calomel ointment (in the proportion of 1 to 3). The details given in regard to these two cases are so incomplete that we cannot properly criticize them.

“In the second case, there were two sexual connections in the space of two weeks, each of which was followed by the use of calomel ointment. The primary lesion occurred twenty-seven days after the first of these connections. It is, however, well known that the incubation period of syphilis is sometimes much

longer (we have seen it extend to fifty-six days in one of our experiments); we cannot, therefore, determine whether the infection does not date from a previous connection.

“ Even definite and complete observations, however, can in no way destroy the results of experiments carried out under such infinitely superior and more reliable conditions.

“ I cannot accept the statement advanced by Prof. Gaucher, who states that it is only ‘ positive ’ cases which should be taken into account in a scientific research.

“ We should then be compelled to admit that antirabic and other vaccinations are useless, because there are cases where the disease occurs in spite of their employment; the same thing might be said concerning the prophylaxis of malaria by quinine, preventive serotherapy against diphtheria, etc.

“ We need not discuss the case quoted by Lévy Bing, of a person who contracted the disease in spite of the use of corrosive sublimate. We have already shown in our experiments that it is an antiseptic which is useless for this purpose, and we have, therefore, never recommended its use.”

## APPENDIX II.

*The result of a series of later researches.*

MM. METCHNIKOFF and ROUX have been kind enough to supply us with a summary of their latest researches on the prophylactic use of calomel ointment.

From the month of October, 1906, they had felt convinced that the preventive power exerted by the ointment was not influenced by the time spent in rubbing, but rather by the amount of calomel contained in the ointment. This explained the results obtained by Prof. Neisser.

They have since carefully studied the question of the excipient, and have tried to modify it. Lanolin possesses such a firm consistency at a low temperature, that its use in winter is difficult.

The addition of water reduces the consistency of the ointment, but destroys its preventive action.

The best results up to the present have been obtained by the substitution of vaselin for lanolin in the proportion of 10 per cent of the total mass. This proportion should not be exceeded, nor, indeed, should vaselin be ever totally substituted for lanolin, as it has been found that calomel ointment prepared in this way exercises no preventive influence.

The following facts have been definitely settled:—

1. The proportion of calomel in the ointment should never be less than 25 per cent; 33 per cent is preferable.

2. The best excipient is lanolin mixed with a small quantity of vaselin (10 per cent maximum).
3. Lanolin and vaselin must be anhydrous.

As a result of the experiments carried out at the Pasteur Institute, many chemists have advertised and sold to the public so-called prophylactic ointments against syphilis.

Some with criminal carelessness have had no hesitation in modifying, according to their own fancy, the ingredients of the ointment ; whilst others have found it simpler and easier to sell the ordinary calomel ointment of the *Codex*. As this latter, besides containing calomel in insufficient quantities, has vaselin for its excipient, it is absolutely useless for the purpose. For the above reasons, we desire to state again that the following is the formula recommended by MM. Metchnikoff and Roux :—

|   |                    |    |    |        |
|---|--------------------|----|----|--------|
| R | Calomel            | .. | .. | 33 gr. |
|   | Vaselin, anhydrous | .. | .. | 10 gr. |
|   | Lanolin            | „  | .. | 67 gr. |

This ointment should be used within eighteen hours after any danger of infection. The infected parts should be thoroughly rubbed, so as to spread the ointment wherever the virus may have penetrated.

## APPENDIX III.

BY F. L. DE VERTEUIL.

## ANTI-SYPHILITIC VACCINATION.

As soon as it had been definitely established that syphilis could be communicated to the simian species, the question of conferring immunity against the disease naturally presented itself to experimenters on the subject.

To accomplish this, two main lines of research were open. The first consisted in rendering the human organism refractory to the disease by means of the serum of an immunized animal. All attempts at doing this have hitherto failed ; the animals which have been tried for the purpose have never produced a serum capable of conferring immunity.

It has also, up to the present, been found impossible to obtain a vaccine by killing the virus or modifying it by means of chemical or physical agents.<sup>1</sup>

The second method was to try and attenuate the human virus by passage through the inferior apes, in such a manner that this attenuated virus, inoculated to man, would produce merely a simple local lesion like

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<sup>1</sup>MM. Metchnikoff and Salmon (*Acad. de Méd.*, 7 June, 1907) have, however, succeeded in aborting the disease in a monkey, eleven days after inoculation, by means of an injection of a 10 per cent solution of atoxyl (anilarsenate of sodium). The animal received an injection of 0.5 cgram of atoxyl, which was repeated forty-eight hours afterwards.

that of ordinary vaccination, and which would confer immunity against the disease.

Metchnikoff and Roux chose for the purpose of the experiment the *Macacus rhesus*, as this species is much more refractory to the disease than *M. cynomolgus* (Java macaque) or *M. sinicus*. Out of ten rhesus macaques inoculated by these experimenters, only four contracted the disease after a period of incubation varying from seventeen to twenty-four days.

They have succeeded in perpetuating a syphilitic virus in the rhesus, and have now got as far as the twenty-second passage. They obtained two rhesus monkeys inoculated by MM. Finger and Landsteiner, of Vienna, one of which represented the eighth and the other the ninth passage of the virus. After the eighth passage the virulence of the virus had almost disappeared. In order to reinforce its virulence, Metchnikoff and Roux commenced by inoculating a chimpanzee with syphilitic material taken from these two rhesus monkeys. The chimpanzee was severely affected, manifesting well marked primary and secondary lesions. The virus from this chimpanzee was subsequently passed from rhesus to rhesus without interruption. During the series of passages the period of incubation progressively diminished from nineteen to seven days. The curious fact to note was that after the passage of the virus through the chimpanzee, it became more and more virulent for the rhesus species. On the other hand, it had little or no effect on an allied species, the *Macacus cynomolgus*, while it had *completely lost its virulence* in the case of the chimpanzee, the most susceptible of all to the disease. In fact, by

the time the eleventh passage had been reached, it had already lost its virulence for this last animal. The fact that the virus in the rhesus still remained of a genuine syphilitic nature was confirmed by the discovery of the spirochæte of Schaudinn.

"We have not," say MM. Metchnikoff and Roux, "inoculated the virus of this rhesus in man; the fact, however, that it is harmless to the chimpanzee after the eleventh passage, leads us to think that it would be equally so to man."

There is no doubt that the first step in the production of a vaccine has been attained, viz., the attenuation of the virus. The question yet remains to be settled whether this attenuated virus would prove harmless to man.

MM. Metchnikoff and Roux (*Annales de l'Institut Pasteur*, Oct., 1906) give the details of two very interesting cases, which they bring forward as proof of their contention.

*Case I.*—A laboratory assistant who was constantly handling the infected animals, and was therefore exposed to the risk of infection, discovered a small round ulceration on his lower lip, which lasted for a few days and then disappeared without causing the slightest glandular enlargement or any suspicious symptom. On account of the anxiety which the assistant manifested, some scrapings were taken from the sore and injected into a *M. cynomolgus*. The whole incident had almost been forgotten, when after an incubation period of thirty-five days, the macaque presented two typical and well-marked syphilitic chancres on both eyebrows, in which numerous spirochætes could be found.



He was then carefully examined by Prof. Fournier, the eminent authority on syphilis, who unhesitatingly pronounced him to be quite free from the disease. He was kept under observation for six months, and not the slightest sign of the disease manifested itself. Moreover, MM. Metchnikoff and Roux declare that they have strong reasons for accepting the man's statement that he had never previously suffered from syphilis.

In order to throw some further light on the nature of the virus, seventeen anthropoid apes and monkeys, including three chimpanzees, were inoculated with scrapings from the sore. All the monkeys developed typical primary lesions, but none of the chimpanzees manifested any secondary symptoms. It was also found that animals successfully inoculated resisted subsequent inoculation with ordinary human virus. This points clearly to an attenuation of the virus, which was below the average virulence of human viruses.

This experiment is open to several objections. The most important point remains an unknown quantity, viz., the time at which the inoculation of syphilitic virus from the monkey took place. Did, indeed, this inoculation really ever take place? Unknowingly, the assistant may have previously contracted the disease, of which these sores were the manifestations.

*Case II.*—A woman, age 79, who voluntarily offered herself for the purpose of inoculation, was, in the month of August, 1905, injected in the fore-arm with virus which had passed through five monkeys. On the same day this virus was inoculated in a chimpanzee and a *Macacus sinicus*, both of which contracted the disease. The woman, on the other hand, exhibited only the most

insignificant lesions. There developed at the points of inoculation, after twelve days, two small, slightly raised papules, which disappeared at the end of six weeks. These did not give rise to any lymphatic enlargement or to any other syphilitic manifestations during the whole year she was kept under observation.

This experiment tends to prove that the virus had been attenuated for the human subject, though it was still virulent for one of the anthropoid apes, the animal most closely related to man.

Though the patient denied in all good faith ever having previously suffered from syphilis, it is almost impossible to entirely exclude the possibility of her having done so.

These results naturally require confirmation and further proofs before they can be finally accepted. The more important the result of an experiment, the more stringent should be the proofs furnished of its truth.

Though an anti-syphilitic vaccination has not yet come within the realms of practical therapeutics, a large amount of very valuable work has been done, which augurs well for the future. Experiments are at present being carried out in many laboratories in different parts of the world. Neisser,<sup>1</sup> who had already

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<sup>1</sup> We learn (Jan. 1908) that Prof. Neisser has just returned from Batavia. From a large number of experiments he has come to the following conclusions:—

1. It is impossible to obtain a serum that will produce immunity.
2. A radical cure of the disease is possible by treatment with mercury and iodide, as well as atoxyl.
3. The serum diagnosis is useful, and affords a reliable test of complete cure. He successfully inoculated apes which had been infected twice before and twice cured.

spent a year in Java, where he had inoculated over a thousand monkeys, has again returned to the same centre, and during the course of last year he has been actively occupied in carrying out experiments on the subject.

“ Though the results obtained may appear to be out of proportion to the amount of arduous work already done, they are nevertheless encouraging. It is but a short time ago that the whole subject entered into the experimental stage. We should not forget that until a few years ago it was considered almost a dogma that the disease could not be transmitted to animals, that the causal organism was unknown, that everything in the study of syphilis depended on pure empiricism.”<sup>1</sup>

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<sup>1</sup> Bayet, *Le Microbe de la Syphilis et les Essais de Vaccination*, 1907.

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